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Studying Fluid Status and the Dying - The Challenge
of Clinical Research in Palliative Care

by

Raymond A. Viola, M.D., C.C.F.P.

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the School of Graduate Studies and Research
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Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa
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Raymond A. Viola, M.D., C.C.F.P., 1996.



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ABSTRACT

INTRODUCTION: The use of parenteral fluid therapy for dying persons who no longer drink adequately is controversial. The issue is important and has wide relevance to any health care setting which provides care for the terminally ill. Benefits and harms from fluid volume depletion and from fluid therapy are argued, but good evidence is lacking. The investigation of the effects of fluid status and fluid therapy on the dying illustrates some of the obstacles to doing palliative care clinical research. Although all clinical settings pose impediments to research involving patients as participants, palliative care faces obstacles which are particularly relevant to this setting. By recognizing obstacles and considering them in planning specific studies or overall research agendas, strategies can be formulated to deal with them, clinical research in palliative care can progress and solutions to clinical problems can be found.

OBJECTIVES/METHODS/RESULTS:

Fluid Status and Fluid Therapy

Objectives: To investigate the effects of fluid status and fluid therapy on the dying (Fluid Status Study).

Design: (1) Systematic review of the health care literature for background material; (2) Experimental, nonrandomized, open comparative study.

Setting: Two inpatient palliative care units (PCUs), one in Ottawa (Ott) and one in Edmonton (Edm).

Sample: Consecutively admitted advanced cancer patients who were able to give informed consent, as determined by a score of 24 or more on the Mini-Mental State Examination (MMSE) and by subjective competence, were considered. Each PCU assembled one of the comparison groups. Out of 288 patients assessed, 123 were approached for participation and 94 consented. These were followed in Phase I until 70 were at clinical risk of developing a fluid deficit and started the main phase of the

study (Phase II); 24 patients never reached Phase II. Out of the 70 patients, two were excluded from Phase II and two were not evaluable due to large amounts of missing data. There were 33 evaluable Phase II patients in each group. In Ott, all 33 patients died in Phase II, while in Edm 27 died in Phase II.

Interventions: Hypodermoclysis was given to all Phase II patients in Edm to maintain optimal fluid balance. No parenteral fluids were administered to Phase II Ott patients. Patients remained in Phase II until their risk of fluid deficit resolved for 10 days.

Main outcome measures: Visual analogue scale (VAS) scores for 12 symptoms; MMSE; Delirium Rating Scale (DRS); level of consciousness; constipation; vomiting; pressure ulcers; edema; myoclonus; oral mucosal hydration; skin turgor; 24 hour fluid balance; 24 hour urine output; heart rate; blood pressure; serum urea-to-creatinine ratio; serum creatinine; serum sodium.

Results: Descriptive statistics using parametric and non-parametric methods were used to compare the groups over time. Missing data were prominent. The groups showed differences in indicators of fluid status including fluid balance, urine output, urea-to-creatinine ratio, skin turgor and heart rate, with all indicators consistent with poorer fluid status in the Ott group. The groups displayed differences at the start of Phase II in several symptom-related outcomes - level of consciousness, MMSE, DRS, weakness, thirst, prevalence of pressure sores and prevalence of edema. Ott was worse than Edm in all these measures. Median survival in Ott from the start of Phase II was four days, and in Edm was 31.5 days. Because of the lack of baseline comparability, further comparisons were made relative to the day of death. From this perspective, both groups showed deterioration in cognitive status close to death, but Ott's group may have deteriorated a few days before Edm's. DRS scores were consistently worse

in Ott, yet both groups' scores worsened during the two weeks before death. Proxy scoring of the VASs was needed equally in both groups, and was required by about 90% of the patients near death. Myoclonus was more prevalent in Ott as were pressure ulcers, but there were no differences in level of consciousness or prevalence of edema. Drugs with sedating effects and with anticholinergic effects were used more often in Ott while corticosteroids and oxygen were used more in Edm.

Relevant obstacles faced while doing this study included: negative attitudes of staff towards research; ethical concerns; cognitive impairment of patients; and the poor and unstable condition of patients.

Obstacles to Palliative Care Clinical Research

Objectives: To further identify clinical research obstacles which are particularly relevant to palliative care and strategies for dealing with them.

Design: Systematic survey of selected journals.

Sample: Palliative care clinical studies published in 1992 and 1993 in three journals: Journal of Palliative Care; Palliative Medicine; and Journal of Pain and Symptom Management.

Results: Sixty-nine studies were identified. Only eight included comparison groups and six of these were randomized trials. Single group and retrospective studies were prominent. Twenty-five were therapy studies and the rest were evenly distributed amongst other categories of research purposes. No source of funding was indicated for 67% of studies. When funding sources were reported and the type of source was clear, only 26% were research funding agencies or government sources. Obstacles were identified and classified into four main categories: problems caused by the patients' poor and unstable conditions; ethical concerns; population heterogeneity; and lack of relevant outcome measures. These potentially affected the following: recruitment; informed consent; participation; use of investigations; assessment of

outcomes; internal and external validity; and choice of research design. A narrative description of the identified obstacles was provided along with explanations of strategies used by the investigators to deal with them. The information collected was combined with the first-hand experience of facing obstacles while planning and conducting the Fluid Status Study to compile a more complete list of obstacles to palliative care clinical research.

CONCLUSIONS: Clinical decision-making regarding fluid therapy must remain individualized. In clinical research, fluid status indicators could include intake and output measures and the serum urea-to-creatinine ratio. There is still a need to identify the population of terminally ill patients for whom uncertainty exists regarding the use of fluid therapy. Once that is done, a randomized controlled trial to evaluate fluid therapy for the dying should be done. This should include some or all of the following outcomes: mental status, opioid toxicity, pressure ulcers, thirst and dry mouth, quality of life and family impact. Survival should be a secondary outcome. Basic science research is needed to investigate the metabolism of water by the dying.

Relevant palliative care research obstacles include: negative attitudes; ethical concerns; lack of research expertise; lack of funding; the poor condition of patients; lack of a clear population definition; population heterogeneity; limited patient access; and lack of relevant outcome measures. Education and involvement of staff is needed as is ethical monitoring of studies. Community participation in research planning should be increased. Collaborative research networks are needed to facilitate multi-centre trials. Pilot studies prior to major studies should be considered. The progress of palliative care research can be monitored by repeating surveys of research at intervals of time.

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LIST OF ABBREVIATIONS

a.m.	morning
adm	admission
AIDS	Acquired Immunodeficiency Syndrome
AMTS	Abbreviated Mental Test Score
BM	bowel movement
bp	blood pressure
bpm	beats per minute
CI	confidence interval
desc	quantitative-descriptive analysis
DRS	Delirium Rating Scale
Ed	Edmonton
Edm	Edmonton
ESAS	Edmonton Symptom Assessment System
GI	gastrointestinal
HDH	hypodermoclysis
Hg	mercury
IMS	impaired mental status
inf	quantitative-inferential analysis
IV	intravenous
JPC	Journal of Palliative Care
JPSM	Journal of Pain and Symptom Management
l	litre
lab	laboratory
LOC	level of consciousness
LOS	length of stay
M/F	male/female
max	maximum
mEq	milliequivalent
mg	milligram
min	minimum
ml	millilitre
mm	millimetre
mmol	millimole

MMSE	Mini-Mental State Examination
mOsm	milliosmole
n	sample size
narr	narrative analysis
NHS	National Hospice Study
NS	non-significant
Ot	Ottawa
Ott	Ottawa
p.m.	evening
PCA	patient controlled analgesia
PCP	primary care person
PCU	palliative care unit
PM	Palliative Medicine (journal)
prn	as needed
QOL	quality of life
RCT	randomized controlled trial
REB	research ethics board
ref	reference
SD	standard deviation
STAS	Support Team Assessment Schedule
U.K.	United Kingdom
umol	micromole
VAS	visual analogue scale
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 STATEMENT OF PROBLEM

The burden of suffering experienced by the dying is substantial, consisting of multiple, often complex physical symptoms as well as psychological and spiritual distress^{1,2}. Although palliative care services were established to provide care for the dying in general, the vast majority of recipients of this care up to now have been dying cancer patients and their families³. Cancer accounts for about one quarter of all deaths in Canada⁴. It is estimated that 61,800 persons will die from cancer in this country in 1996. There will be about 129,200 new cases during that year⁵, with over 50% of these patients eventually dying of their disease. Largely due to the aging of the Canadian population, the number of new cases and deaths from cancer will continue to rise, and will likely reach 70,000 to 75,000 deaths per year in the year 2000⁶. Persons dying from Acquired Immunodeficiency Syndrome (AIDS) and other active, progressive diseases add to the total requiring palliative care.

Modern day palliative care was born 30 years ago out of concern for the perceived plight of the dying in a highly technological health care system. Two extremes of care appeared to be provided to these patients: one consisted of heroic attempts to prolong life using increasingly futile technological interventions until death; the other consisted of almost complete neglect of the patient's care with the explanation that "nothing more can be done"^{7,8}. Palliative care principles and practices evolved from observing these two extremes of practices and believing that a better way of providing care for the terminally ill was possible. The use of medical technologies was generally discouraged, including relatively simple ones like parenteral fluid therapy for patients who stop drinking⁹. Evidence to support this and

other management practices have come primarily from clinical experience rather than from controlled clinical trials or well designed observational studies¹⁰.

The use of parenteral fluid therapy is one example of several controversial treatment approaches used in palliative care. For this therapy, the controversy extends beyond palliative care to the care of the dying in different health care settings; therefore, the issue has wide relevance. It is believed by many palliative care clinicians to offer no benefit and potentially to cause harm to the large proportion of dying patients who stop drinking as death approaches. They also maintain that there are benefits to some dying patients if they become fluid volume depleted¹¹. This belief contrasts with the practices in the general medical and nursing communities outside of palliative care where the use of artificial means of providing fluids to dying patients is more common¹². The belief that the dying require fluid support for comfort is held by a large proportion of these clinicians¹³. Little good evidence supports either viewpoint. Recently, some palliative care clinicians have questioned the long-held palliative care teaching on this issue, and have reported their practice of offering fluid therapy to most dying patients under their care¹⁴.

Fluid therapy is usually delivered by intravenous infusion of fluids or by a simpler technique called hypodermoclysis (HDC), the infusion of fluids into the subcutaneous tissue¹⁵. Although the intervention is relatively easy to deliver, the risk-benefit ratio is uncertain with respect to quality of life and survival. In addition, the issue is complicated by a combination of important physical, psychological, social, spiritual, ethical, and legal aspects to the debate. It is not only the dying patient who is potentially affected, but also the bereaved family and friends and the professional caregivers^{16,17,18}. Clinicians are looking for valid evidence to support

recommendations one way or the other.

The pursuit of clear, unbiased answers to questions about the management of the dying is complicated by the environment in which such studies must be carried out. Research in palliative care has lagged behind advances made in other areas of the field. Much interest exists in increasing the amount and the quality of clinical research that occurs, but there are impediments to accomplishing this¹⁹. Although every clinical setting poses obstacles to the performance of research, there may be some obstacles which are particularly relevant to palliative care. By identifying these, it may be possible to minimize or even eliminate some of the obstacles. Others will need to be considered and accommodated when planning studies or overall research agendas.

The burden of suffering from terminal illness is great and growing and the clinical problems faced are severe and often urgent. There is no clear agreement on many of the therapies involved, such as parenteral fluid therapy, yet there is a growing demand for solutions. Obstacles to research in palliative care are impeding the progress of research; innovative solutions must be found so that research can improve in quality and quantity.

1.2 CONTRIBUTION OF THESIS

This thesis contributes to palliative care in the following ways:

- (1) It summarizes in a systematic way the clinical evidence that has existed until now regarding the effects of fluid status and fluid therapy on the dying, which is a common, important and controversial clinical topic;
- (2) It contributes to the evidence available regarding the effects of fluid status and fluid therapy on the dying;
- (3) It suggests questions requiring further research regarding the effects of fluid status and fluid therapy on the dying;

- (4) It assists with the methodological planning of future studies of the effects of fluid status or fluid therapy on the dying;
- (5) It identifies obstacles which are particularly relevant to performing clinical research in palliative care generally;
- (6) It suggests strategies for dealing with identified relevant obstacles to palliative care clinical research, which has been impeded in both quantity and quality; and
- (7) It illustrates the methodology of the systematic literature review for performing reviews of palliative care clinical topics.

1.3 OUTLINE OF THESIS

In this thesis three studies are reported. First, a systematic review of the health care literature presents the evidence available pertaining to the clinical problem of the effects of fluid status and fluid therapy on dying patients. It was not simply a review of the literature, but a structured, systematic review modelled after methodologies for performing meta-analyses. Since the clinical studies identified by the systematic review were small in number and of generally low methodological quality, obstacles to the conduct of clinical research in palliative care are reviewed next. As part of this background, these obstacles are illustrated by the identified fluid studies. The combination of the systematic review and the discussion of research obstacles sets the stage for the presentation of the clinical trial, including the rationale for the methodologies chosen.

Second, the study of the fluid volume status of cancer patients admitted to two palliative care units (PCUs) is reported. This was the first controlled study to evaluate the effects of fluid therapy on the dying. It used an experimental, nonrandomized, comparative design to follow two parallel cohorts, one receiving and the other not receiving

fluid therapy. Multiple outcome measures were assessed to compare the two groups with respect to fluid status, symptoms and other treatments. The limitations of the study are discussed, the results are interpreted and compared to previous studies and recommendations pertaining to further research are made. Obstacles faced throughout the process of planning and conducting the trial are reviewed.

Third, obstacles relevant to palliative care clinical research in general are explored by means of a survey of three palliative care journals over a recent two year period. All clinical studies were identified using explicit criteria. They were reviewed with the goal of compiling a representative collection of barriers to palliative care research and obtaining an overview of the type of research occurring. Only obstacles particularly relevant to palliative care were identified. Their possible effect on the choice of research design was considered as well. A set of obstacles faced by palliative care researchers are presented and some strategies for dealing with them suggested.

Finally, the information obtained with respect to the effects of fluid status and fluid therapy on the dying and obstacles to palliative care research are summarized. Clinical and research recommendations are made and some general strategies for dealing with the obstacles are suggested.

CHAPTER 2

BACKGROUND

2.1 SYNOPSIS

A structured, preplanned, systematic review of the English language health care literature is presented in which published clinical studies investigating the effects of fluid status or fluid therapy on dying patients were sought and reviewed. The goals were to ascertain what clinically relevant, published evidence existed and to assess the strength of this evidence. The information was meant to be used to inform clinicians on optimum clinical practice and to provide direction for further research by helping generate hypotheses and by highlighting methodological issues.

Because of major limitations present in the small number of studies included in the review, it is followed by a discussion of obstacles to clinical research in palliative care. These obstacles provide a challenge to doing palliative care clinical research and could impact on the type, quantity and quality of research that is carried out. They are placed into perspective by considering the history and development of palliative care in general. Those that may have been important in the studies included in the review are discussed to illustrate some of the issues.

By the end of this chapter the state of knowledge pertaining to the effects of fluid status and fluid therapy on the dying is summarized, questions requiring further research are suggested, and some obstacles to palliative care research are identified. These are all relevant to the clinical trial that is reported in Chapter 3 and the broader examination of obstacles challenging palliative care clinical research, which is presented in Chapter 4.

2.2 A SYSTEMATIC REVIEW OF PUBLISHED CLINICAL RESEARCH ON THE EFFECTS OF FLUID STATUS OR FLUID THERAPY ON THE DYING

2.2.1 Introduction

The World Health Organization defines Palliative Care as:

... the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best possible quality of life for patients and their families.²⁰

The suffering experienced by dying persons has multiple causes²¹. The role of fluid volume status as a factor in the etiology of this suffering is poorly understood and its importance remains controversial - polarized views exist, even amongst those working in the field of palliative care²².

The use of intravenous (IV) fluids for dying persons appears to be common in hospitals. In one study, of 106 patients who died of cancer in hospital and who were retrospectively reviewed, 86 (81%) received IV fluids within the last 30 days of life and 73 (69%) died with an IV in place²³. Similarly, a decision by physicians to discontinue such therapy, once instituted for a critically ill individual, seems to be unlikely, even when the decision to withdraw life support has been made. IV fluids were the least likely form of life support to be withdrawn out of eight treatments in one survey of hospital physicians²⁴.

Moderate to severe fluid depletion in the non-terminally ill patient can result in symptoms of lethargy, weakness, confusion or obtundation. If electrolyte abnormalities are present hyperexcitability can occur as well, manifested by muscular twitching, irritability and seizures²⁵. Other symptoms associated with fluid deficiency include the following: thirst; dry mouth; dysphagia; apathy; depression; headache; nausea; vomiting; and muscle cramps²⁶. There is

evidence that the elderly have a reduced thirst sensation²⁷. Poor fluid intake has also been suggested as a risk factor for the development of pressure ulcers of the skin²⁸.

One of the generally accepted beliefs amongst palliative care clinicians since the modern era of palliative care began in 1967 has been that artificial fluid therapy is usually unnecessary for the dying person who is unable or unwilling to drink. The observation of patients near death suggested that artificial fluid therapy offered little benefit and the potential for harm. In fact, fluid volume depletion was seen as beneficial to the patient close to death; decreased drinking was considered 'natural'²⁹. The important fluid-related needs were believed to consist primarily of feelings of dry mouth and possibly thirst, both of which were felt to be adequately managed by good mouth care and sips of fluids as tolerated³⁰. Neuromuscular irritability, restlessness³¹, lethargy, drowsiness and fatigue³² were acknowledged as potential consequences of a fluid deficit; however, they were thought to be either easily managed by other means or of little importance as sources of distress. Postural hypotension was considered of some importance if an ambulatory patient was symptomatic. In such a case some clinicians would have considered fluid therapy³³. The presumed benefits of fluid deficiency included: decreased pulmonary secretions resulting in less dyspnea and coughing; decreased saliva production resulting in less choking and drowning sensations; decreased urine production resulting in less incontinence and less need for assistance with voiding or catheterization; decreased gastrointestinal (GI) tract secretions resulting in less nausea and vomiting³⁴; decreased peritumoral edema resulting in decreased pain; and decreased edema and ascites^{35,36}. Evidence to support these beliefs and the practice of not usually providing parenteral fluids to the dying consisted of clinical experience, opinion and anecdote.

If decreased level of consciousness was associated with

a fluid deficit, this was felt to be beneficial since the person's perception of suffering would decrease at the same time³⁷. A fluid volume deficit was believed to be associated with general analgesia as well. Some postulated about the possible role of accumulating ketones and of increased production of endogenous opioids in producing this apparent effect in patients who were volume depleted and malnourished³⁸. These hypotheses were based on animal experiments.

The use of fluid therapy was believed to potentially produce the opposite effects to those listed above, aggravating symptoms experienced by the patient. In addition, there was concern that fluid therapy could cause psychosocial effects including: increased emotional distress in the family³⁹; diversion of the carers' attention from the patient to the monitoring of the infusion⁴⁰; fueling of denial of the patient's condition; and interference with interactions between the patient and family due to the presence of the technical apparatus⁴¹.

Recently, this traditional palliative care point of view was challenged from within palliative care. Clinician-researchers noted that some common problems faced by the dying, such as delirium, could be associated with fluid volume depletion. They were concerned about the various metabolic effects of volume depletion and the potential for renal failure to occur, resulting in the accumulation of drug metabolites. In particular, they noted that with renal failure there was an increased risk of toxicity from the accumulation of opioid metabolites, possibly causing confusion, myoclonus and seizures. They were also concerned that fluid deficiency could result in an increased risk of pressure ulcers of the skin and constipation⁴². They reported that the standard of care in their palliative care unit was to offer HDC to all patients who were unable to drink adequately. They saw this as a simpler method with advantages

over the IV route from a technical and practical point of view⁴³.

Others have argued for the provision of fluids to the terminally ill on ethical, legal and social grounds^{44, 45, 46}; the debate is complicated by these wider issues. Because of the apparent lack of good evidence to support any therapeutic approach, several authors have simply suggested that decision-making pertaining to the use of fluid therapy for the dying be 'individualized'^{47, 48, 49}.

In reviewing the literature on the effects of fluid status and fluid therapy on the dying, one approach is to use the methodology developed for performing systematic reviews. These have been used especially for reviews of randomized controlled trials and have been defined as:

...the application of scientific strategies that limit bias to the systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic⁵⁰.

Non-systematic reviews examining fluid status effects on the dying are numerous. In preparing a review, there is potential for bias to affect the identification and selection of articles, the weight put on each of the articles included, the information extracted and presented, the combining of the information from all the sources used, and the conclusions drawn. Usually little attention is paid to the strength or quality of the evidence presented in the various articles cited. A systematic approach may not eliminate bias completely, but it makes visible all components of the review process, and hence all remaining potential sources of bias. The principles involved in preparing systematic reviews can be applied to reviews in general, even if no randomized trials exist examining the topic of interest.

This section reports the results of a systematic review which examined fluid status effects on the dying.

2.2.2 Goals and Objectives

The goal of this review was to use a systematic approach to search the health care literature to identify published studies which assessed the effects of fluid status or fluid therapy on the dying and then to systematically appraise these studies and synthesize their results^{51,52}. The review's objectives were:

- (1) to compile, with a reasonable degree of certainty, a complete list of all known, published, English language clinical studies on this topic;
- (2) to place the quality of the studies identified into perspective with respect to the level of evidence they provide for informing clinical decision making and for formulating hypotheses for further research;
- (3) to outline, in as unbiased a way as possible, the state of knowledge that exists on this topic based on clinical research carried out with dying patients;
- (4) to identify hypotheses or questions for further research; and
- (5) to identify factors which may help in the planning and design of future research on this topic.

2.2.3 Methods

Eligibility Criteria

An article was included if it:

- (1) was published in a biomedical journal;
- (2) was an original article reporting the results of a specific study;
- (3) dealt with, as a main focus, the possible effects of fluid status or fluid therapy on patients;
- (4) involved human patients described as dying or terminally ill, or as receiving hospice care, palliative care or terminal care;
- (5) reported outcomes derived from the assessment of patients;

- (6) reported clinical outcome measures other than or in addition to laboratory data; and
- (7) was published in English.

An article was excluded if it:

- (1) reported on a survey of attitudes or opinions of caregivers only;
- (2) reported a case study only;
- (3) reported a case series, with no grouping of results; or
- (4) was a redundant publication of a study (in this case the most complete report of the study was included, or the earliest report in the case of identical publications, and all others were excluded).

The review was limited to English language articles for the following reasons: language translation resources were not available; resources for retrieving more obscure journals were limited; and the main journals in the world dedicated to palliative care were published in English.⁵³ No restrictions were placed on research design, except as indicated above. No specific intervention was sought or required and outcome measures were not specified in advance. Also, diagnosis was not restricted. The search was limited to published studies because: the expectation was that existing studies were small in number and generally weak methodologically; the resources available to search extensively for unpublished material were limited; and a search for unpublished studies would have been nonsystematic and likely futile⁵⁴.

Prior to commencing, the expectations were: the number of studies was small; the sample sizes were small; the studies used a variety of methodologies (likely not including the randomized controlled trial (RCT) design); different populations of palliative care patients were represented in different studies; specific fluid therapy interventions were not always used and when used differed between studies; and different outcomes were assessed in the various studies.

Search Strategy

The studies were identified using the following methods:

- (1) a systematic search of MEDLINE (a computer-based, biomedical literature database created and maintained by the United States' National Library of Medicine) from 1966 to March, 1996 using the Medical Subject Headings (MeSH) and text words (txt) "palliative care" (MeSH), "terminal care" (MeSH), "symptom control" (txt), "dehydration" (MeSH), "fluid therapy" (MeSH), and hydration (txt), and limited to English only. This search was initially set up and executed by a librarian, in conjunction with the reviewer, although the search was updated by the reviewer;
- (2) a systematic search of CINAHL (Cumulative Index to Nursing and Allied Health Literature) from 1982 to February, 1996 using the same keywords as for MEDLINE plus "terminally ill patients" and "hospice care", and limited to English only. This search was set up and executed by the reviewer;
- (3) a systematic search of CURRENT CONTENTS (which provides computer access to tables of contents of current issues of journals covering many disciplines) from week number 27 of 1995 to week number 15 of 1996 using the search words "palliative care", "terminal care", "hospice", "dying", "death", "symptom control", "terminally ill", "dehydration", "hydration", "fluid therapy", "intravenous fluids", "hypodermoclysis", "fluid status", and "water", and limited to English only. This search was set up and executed by the reviewer;
- (4) a search of reference lists of included articles and of other related articles, including reviews, letters, editorials, commentaries and related research articles;
- (5) hand searching of 6 palliative care journals, from each journal's first issue until the most recent available issue (see Table A.1);

- (6) a search of 11 selected books (see Table A.2), along with relevant reference lists contained; and
- (7) contacting experts in the field, known to the reviewer or identified through publications, to confirm completeness of the search.

EMBASE, the computer-based version of Excerpta Medica, a European health sciences literature database overlapping MEDLINE by about 30%⁵⁵, was not included in the search strategy because of its high cost and the low chance of identifying any additional pertinent studies. No attempt was made to systematically locate and search proceedings of conferences and symposia, although some were examined if they were published in one of the manually searched journals. This and other forms of "grey literature" (material semi-published in the form of reports such as research reports, policy documents, dissertations, and theses) were not included in the search strategy because of the difficulty in accessing this literature in a comprehensive and systematic way⁵⁶, the lack of resources to try to do this and the low likelihood of identifying additional eligible studies.

Due to the lack of resources, the selection process was carried out by one person only, so reproducibility was not assessed. No blinding of authors' names, study locations, source journal, or results was done. Based on the title and the abstract, when available, the full text of any article potentially meeting the inclusion criteria was retrieved and examined before a final decision on eligibility was made. The explicit eligibility criteria were followed closely when considering each of the retrieved articles. Any contentious issue regarding the eligibility of an identified paper was discussed with the thesis supervisor and resolved by consensus.

Assessment of Methodological Quality

Methodological quality of an included article was

assessed independently by two people, the reviewer and a research assistant familiar with research methodology quality assessment. There was no blinding of the authors' names, study locations, source journal, or results. Where disagreements existed in the scoring, resolution occurred by consensus. The instrument used to assess methodologic quality underwent previous validity and reliability testing and was developed to be applicable to a variety of research designs^{57,58}. The instrument is shown in Table A.3. The definitions used for design terminology are given in Table A.4⁵⁹ and the scoring system applied to the instrument is in Table A.5 (personal communication, M. K. Cho). Scores could fall between zero and one, with one representing the highest methodologic quality.

Data Extraction

Data was extracted from each eligible article in an unblinded fashion by one person only, utilizing a data extraction form. Column headings on this form designated the information desired regarding characteristics of the studies, their results and their conclusions. Items included as headings were determined by following the published guidelines for the performance of systematic reviews⁶⁰ and by considering the clinical issue of interest in this review. The form was designed to provide a systematic means of extracting information from the articles in an explicit, unbiased and reproducible way. If possible, authors of included articles were contacted if clarification of aspects of their article was needed.

Data Synthesis

The information obtained from the selected articles was combined in tabular format for presentation of the studies' characteristics, results and conclusions. This allowed for easier comparisons to be made. The table used the same

headings as in the data extraction form, but added a column for reporting the methodologic quality score and another for comments (see Table A.6). A narrative summary was also provided. This approach was planned a priori, anticipating that the studies would not allow for statistical synthesis because of their methodologic quality and clinical heterogeneity. In addition, it was expected that data would be presented in the studies mostly in a descriptive manner. If possible, a quantitative approach to data synthesis was to be carried out and reported as well.

2.2.4 Results

Excluded Studies

Several surveys dealt only with clinicians' opinions on the issue of fluid status or fluid therapy and terminal illness. Several other articles contained only one or more case studies with no grouping of results. No excluded article reported a case series consisting of more than 3 cases. The vast majority of excluded articles discussing this topic were reviews or opinion pieces only, and included discussions of ethical, social and legal issues.

Fifteen publications dealt with pertinent studies, but were excluded. Two contained only laboratory outcome data^{61,62}. Six others dealt only with methods of providing fluids to the dying or reasons for doing so^{63,64,65,66,67,68}. Six more were thought to be redundant versions of five of the included studies. Of these, one was a thesis⁶⁹ that was subsequently published three years later⁷⁰ (the publication included the thesis in its reference list). The other five were abstracts or letters. Four were published prior to the corresponding full article (ranging from 1 to 4 years earlier)^{71,72,73,74}, while the fifth, a letter, was published about a month after the corresponding full paper, but in a different journal⁷⁵. This last one was not clearly redundant because neither the number of patients included nor the

results matched the longer report. Despite this, the authors, the design, the setting and two of the three outcomes measured were the same. Its data seemed to be from a separate study, but due to its brief format as a letter and the possibility of some overlap with the longer publication, it was excluded.

The final excluded article which requires mention was a review article⁷⁶ that summarized a study and gave in its reference a date of 1994, reporting that it had been "submitted for publication". No journal was mentioned. The summary of the study and direct communication with the author of the review suggested that the study would probably have been eligible for inclusion in this review if it had been published. The author of the review article confirmed that the study had not yet been published, but that it was resubmitted for publication.

Included Studies

Six studies were selected for inclusion and all were full articles^{77, 78, 79, 80, 81, 82}. Two (Waller and Musgrave) were published in two different palliative care specialty journals. Three others (Burge, Ellershaw and Bruera) came from a third specialty journal which attracts a significant palliative care readership. The sixth article (McCann) was published in the Journal of the American Medical Association. All articles were published since 1993. Their characteristics are given in Tables A.7 and A.8. Table A.7 shows their design characteristics while A.8 gives information on their assessments and method of analysis as well as their methodologic quality scores. The results and conclusions of each study are shown in Table A.9 along with additional comments.

Methodologic Quality Scores

The mean ($\pm$ SD) methodologic quality score for the six eligible studies was 0.42 ± 0.08 (ranging from 0.36 to 0.58).

Five of the studies had very similar scores, between 0.36 and 0.41, while one study (Burge) stood out receiving a score about 50% higher than the others (0.58). It scored much better than the other five on five questions in particular (numbers 16 to 20 in the instrument). These all dealt with statistical issues - accounting for confounders, justification of sample size, post hoc calculation of power and the choice of statistical analyses. All studies lost two points because they did not select subjects randomly from the target population. All except McCann lost because they lacked blinding (which was felt to be not applicable to McCann's study). McCann lost further because of the lack of control subjects, failure to account for detection bias or confounding, lack of sample size considerations and statistical tests and failure to provide details about subject attrition. Waller did not account for detection bias or confounders, presented no sample size justification or power calculation and made conclusions not supported by the findings. The latter item related to his suggestion that the results "indirectly support, and in part explain, the observation that there is no difference in survival of terminal cancer patients whether they stay in a hospice facility...or in a general medical ward..."). Ellershaw failed to account for detection bias and confounding and gave no sample size justification or power calculation. Bruera did not deal with potential detection bias, sample size or power. Musgrave had no controls and lacked statistical tests, sample size justification and power calculation.

Characteristics of the Studies

The six studies used a variety of basic study designs. Three (Burge, Waller and Musgrave) were cross-sectional surveys (Waller included internal controls), two (McCann and Ellershaw) were prospective, single cohorts (Ellershaw included internal controls) and one (Bruera) was a

retrospective natural experiment in which two historical groups were compared. All were essentially structured to be hypothesis-generating studies whose purposes had a common theme - to look for an association between fluid status or fluid therapy and symptoms in terminally ill patients. To do this they looked at different outcome measures. Most interest was in thirst and dry mouth, assessed by 100 mm. visual analogue scales (VAS) in Burge, dichotomous questions (present/absent) in McCann and Ellershaw, and a four point verbal rating scale in Musgrave. Other outcomes measured, each in only one of the papers, included: discomfort (using a 0 to 10 numerical rating scale) in McCann; alertness (on a 4 point numerical rating scale) in Waller; respiratory tract secretions (dichotomous) in Ellershaw; impaired mental status (IMS), used as a surrogate outcome for delirium, (dichotomous) in Bruera; and ascites and leg edema (dichotomous) in Musgrave. Although Burge measured several other symptoms with VASs, he did not test their association with fluid status.

The total sample size included in all six studies was 532; Bruera included 279 of these. All were inpatients in either a palliative care setting or a hospital oncology unit and all except one (in McCann) had cancer. (Musgrave's patients presumably had cancer too since her study took place on an oncology ward.) Survival differed between studies. Three (Waller, Ellershaw and Musgrave) included only patients who were within days of death. The others included a number of patients who lived much longer. In Burge 73% lived longer than 14 days and some survived several months (the number and the duration were not given). In McCann, the survival spanned 4 to 199 days with a mean of 40 days. In Bruera, 97% died in the PCU and the average length of stay was 33 and 41 days for the two groups assessed.

Three of the articles did not describe or enumerate the excluded patients (Waller, Ellershaw and Bruera). A total of 106 patients were excluded in the other three studies, and

over half were excluded for reasons related to mental status impairment. These excluded patients represented 51% of the total potential subjects (209) for these three studies. Burge described the excluded subjects in his study and showed that there were some significant differences from the included subjects - they had shorter survival, had less fluid intake and required more mouth care assistance.

Artificial fluid therapy was provide to subjects in four of the studies. Burge included some patients who received parenteral fluids (personal communication with F. I. Burge), but gave no information about them. Musgrave included only patients who received IV fluids. Waller compared a subgroup of patients receiving IV fluids to those not receiving any parenteral fluid supplementation. Bruera compared two samples separated in time. The later group existed after three new measures of monitoring and management had been implemented, including more liberal use of parenteral fluids by HDC for patients whose cognitive function declined.

Four studies reported assessments of fluid status. Laboratory tests were used in all four (Burge, Waller, Ellershaw and Musgrave) and fluid output or intake were assessed in two of these studies (Burge and Musgrave). Bruera's retrospective study reported monitoring clinical, urine output and laboratory indices of fluid status, but did not give data for these measures.

Results and Conclusions of the Studies

Three of the studies (Burge, Waller and Ellershaw) reported group laboratory statistics for their study samples. Musgrave gave laboratory results for subgroups of her sample. The means for her total sample could be calculated from the data presented, but not the standard deviations, so these results were not included in the Table A.9. Burge's sample had biochemical measures which were remarkable for their similarity to the reference ranges given while Waller's and

Ellershaw's had more abnormal results. The studies reported different reference ranges for the tests used and different units for some of the measures.

The studies that looked at thirst as an outcome concluded that there was little relationship between fluid status or fluid therapy and the experience of thirst (Burge, McCann, Ellershaw and Musgrave). Burge reported that patients obtained pleasure from drinking and McCann found that symptoms of thirst/dry mouth (combined as one outcome) were always relieved with oral fluids or ice chips or with mouth care, but the duration of relief varied. In Burge's study the VAS scores for thirst ranged between zero and 100 mm, with a median of about 50 mm. The VAS for dry mouth showed a similar spread, but the median was about 60 mm. Musgrave's sample included 12 of 19 (63%) patients whose thirst was rated moderate or severe. Three studies provided data on the prevalence of thirst: McCann noted that it was present in 21 of 32 patients (66%) on admission, but only 12 (38%) retained the sensation until death; Ellershaw reported that 19 out of 23 subjects (83%) who were able to respond reported thirst on the one occasion they were asked within one to five days of death (87% had dry mouth); and Musgrave found that 18 out of 19 (95%) felt some degree of thirst within two days of death.

Waller reported that there was no correlation between the use of IV fluids and the level of consciousness (LOC) of patients, but his data did suggest that poorer states of consciousness were correlated with higher serum sodiums, serum osmolalities and urine osmolalities. Other comments made by the authors were: Ellershaw concluded that respiratory tract secretions were not significantly related to fluid status in the dying; Bruera hypothesized that providing low volumes of fluids to patients who show early signs of cognitive impairment may help prevent agitated delirium from occurring; and Musgrave noted that little relationship was found between the amount of IV fluids received by patients and the

prevalence of edema or ascites.

Meta-analysis

There was little opportunity to perform a quantitative synthesis of data between these six studies given their different designs, populations, interventions and outcome measures. Three of the studies (McCann, Ellershaw and Musgrave) reported data that allowed for the calculation of the prevalence of thirst, given above and in Table A.9. These prevalence data could be considered for statistical aggregation.

Using the prevalence of thirst at admission for McCann's study (66%) and applying the method described by Fleiss for combining proportions³³, the pooled estimate of the prevalence of thirst from the three studies was 86%. The chi square test for homogeneity indicated statistically significant heterogeneity ($X^2=8.98$, $df=2$, $p<0.025$). Clinically, McCann's sample was different from both Ellershaw's and Musgrave's - the subjects in the two latter studies all died within five and two days respectively, while in McCann's study survival was longer, up to 199 days. The prevalence at death was even lower in McCann's study, so statistical heterogeneity would still have existed if that proportion was used instead. It was decided to repeat the meta-analysis using only the studies by Ellershaw and Musgrave. The pooled estimate of the prevalence from these two studies was 91% and the test for homogeneity was non-significant ($X^2=1.658$, $df=1$, $p>0.10$). The 95% confidence interval for the pooled estimate of prevalence of thirst based on these two studies was 82.5 to 99.7%. (This was based on a total of 42 subjects in the two studies.)

2.2.5 Discussion

Limitations of the Review

There were several limitations to this review.

Reproducibility of study selection and information extraction was not assessed and blinding was not used in any of the steps of the review. However, the selection and data extraction processes were systematic and explicit, studies whose eligibility were unclear were discussed with the thesis supervisor and any excluded articles which might have been contentious or at the margins of relevance were listed in this review. This should all have helped to decrease bias and increase the reproducibility of the review.

There was independent scoring of methodologic quality by two reviewers followed by discussion and resolution of disagreements by consensus. Reproducibility was not measured. The instrument used to assess methodologic quality had been previously validated and tested for reliability and was developed to be applicable to a variety of research designs. Its inter-rater reliability was shown to be high³⁴. Although blinded assessment of the quality of study reports has been shown to produce lower and more consistent scores than an open assessment³⁵, the authors of that study stated that this might be important if cutoff scores were recommended to determine eligibility of trials or if quality scores were used to weight the results of the primary studies. Neither of these purposes were relevant for this review; quality assessment was done simply to help characterize and appraise the eligible studies using explicit criteria.

The search was not totally comprehensive - it did not include other databases such as EMBASE, and it excluded non-English studies. No attempts were made to search the grey literature or unpublished studies. The productivity of a more comprehensive search would probably have been low, based on the results of the search that was performed and the history of palliative care research in general (see section 2.3). In addition, limited resources restricted the extent of the review process and searching of the grey literature and for unpublished studies is not well developed at this time.

Whether publication bias is an important issue in palliative care research is unknown, although the field may be at high risk because of the type of research that has occurred (mainly nonrandomized studies with small samples)³⁶.

Limitations and Contributions of Studies

The studies included were small in number and all were published in the last three years. This may reflect the history and development of palliative care and its clinical research. All of the studies had several areas in which bias may have contributed to the results obtained. This was reflected in the generally low methodologic quality scores received, especially for five of the studies. Burge's high methodologic quality score, mainly on the basis of the statistical aspects of the study, suggested a level of planning and analytical sophistication that may have been absent, or at least not reported, in the other five studies. The basic designs of all studies were essentially descriptive; none of the studies were in a position to test hypotheses with their designs.

The study populations included only inpatients, almost all of whom had cancer. They were probably convenience samples for the respective studies. The study populations were not fully described by Waller, Ellershaw or Musgrave and the excluded patients were inadequately described in all papers except Burge. These factors limited comparisons between studies and the generalizability of the results. Burge did show how his excluded subjects differed from the study sample, limiting generalizability of his study. No consensus seemed to exist regarding the population of palliative care patients for whom the question of fluid therapy was uncertain. In particular, prognosis at the time of study entry varied between the studies from days to months, and actual survival varied even more. The palliative care population is heterogeneous with respect to many other factors

as well, such as demographics, terminal diagnoses, comorbidity, treatments, stages of disease, symptoms, psychological condition and social situation (see section 2.3 and Chapter 4). To proceed with further studies, it would be helpful to have agreement on the patient population for whom such research is most necessary, that is for whom uncertainty exists³⁷.

The outcomes assessed in the studies represented only a small number of the potential outcomes relevant to this issue. Thirst or dry mouth were given the most attention. For further useful research to occur, consensus will need to be reached on the important outcomes which need to be assessed related to the effects of fluid status or fluid therapy on dying patients. The studies in this review may provide some guidelines. Waller's and Bruera's studies suggested that mental status may be affected by changes in fluid status and this should be explored further. Thirst and dry mouth deserve continued attention since they were so common and often severe. Their inter-relationship was suggested by McCann, Ellershaw and Musgrave and their etiologies are likely multifactorial. Other outcomes need to be considered as well, such as quality of life (QOL) measures. Relevant tools for assessing QOL in palliative care are being developed and may become the ultimate outcome for this clinical question^{38,39}. The impact of fluid therapy decision making on the family needs to be considered as well.

Blinding was not used in any of the studies. This could potentially have produced bias with respect to the use of alternate treatments (performance bias) or in the assessment of outcomes (detection bias). This appeared to be relevant to all studies except McCann's.

In Burge's study, the narrowness of the range of biochemical measures in the study sample supports the impression that the sample is a specific subpopulation of the terminally ill, especially when the levels are compared to

Waller's and Ellershaw's. The distribution of fluid status levels available may have been inadequate to demonstrate any association with the thirst VAS measures, if a true association does exist, especially with the sample size used. The fluid intake measure used, an estimate by the bedside nurse, was not clearly valid or reliable, a shortcoming Burge acknowledged.

In McCann's study, the methods and results sections implied that some exclusions occurred after entry to the study, if patients became unable to report symptoms for more than 75% of their stay in the unit. These exclusions could have biased the results further because they would have occurred with knowledge of the outcomes available up to that point. Although blinding was not relevant to this study's particular design, detection bias was a real possibility in the team's determination of patient comfort and probably in the patient's expression of thirst as well. Cook et al.³⁰ have listed reasons why uncontrolled observations may result in biased conclusions regarding effects, and several apply to this study. These include: the placebo effect; the patient's wish for success; the clinician's wish for success; and the documented evidence that compliance is a marker for better outcomes, even when a treatment is useless.

In Waller's study, the identification of the internal comparison groups, those receiving or not receiving IV fluids, was open to selection bias. Detection bias when assessing the level of alertness was also possible, since the patient's group was known when the assessment was made. Other treatments given to the subjects were not reported and may have impacted on the results. Details about the IV therapy provided were vague (no information was provided on the duration of therapy or how it was monitored). In the discussion section of their paper, the authors failed to mention the statistical association they found between fluid status markers and alertness, but instead emphasized the lack

of any improvements with IV infusion. Given the potential biases involved and the possibility that the fluid therapy provided was inadequate to correct or maintain optimum fluid status, the association of fluid status and alertness was probably more pertinent and may require further investigation. Of course, a cause and effect relationship, in either direction, were not evaluable in this study.

Ellershaw's study was a mixture of a cross-sectional survey followed by a retrospective review covering the time between the initial assessment and death. Selection bias was possible in assembling the internal comparison groups - it was feasible to clinically assess fluid status and respiratory secretions at the time that recruitment was considered. The inclusion criterion of 'dying' and the exclusion criterion of the patient being 'inappropriate' were both vague. It was possible that respiratory secretions and clinical hydration status contributed to the definition of these two eligibility criteria. As mentioned previously, excluded patients were not described in the report. The completeness, accuracy and interpretation of the follow-up data is of some concern, but the time frame for all patients was less than five days. The prospective outcome measure, respiratory secretions, was already present in over half of the patients at the start of the study. The follow-up assessment of this variable may have been biased by knowledge of the initial assessments, especially fluid status. The definition of 'biochemical dehydration' used was arbitrary and debatable; it may have resulted in the misclassification of some subjects. For instance: an elevation in serum urea could have other causes other than pre-renal failure, including the use of tetracycline or glucocorticoids or the presence of blood in the GI tract; serum urea and creatinine could be elevated because of renal parenchymal problems or post-renal obstruction³²; and hyponatremia can occur secondary to the syndrome of inappropriate antidiuretic hormone (SIADH).

secretion³². With misclassifications, the groups would have been more similar. Also, in the time between the initial assessment and death the two groups likely became more similar with respect to fluid status, which was not reassessed.

In Bruera's study the main potential source of bias was the lack of blinding - the authors did not state whether the chart reviewers were blinded to the time period of the patient. There was also the potential for unmeasured changes to have occurred between the two time periods. Such changes could have included changes in referral patterns, other treatments provided or patient comorbidity. The increase in the sample sizes between the two time periods suggested that some type of change occurred - perhaps in the size of the unit, the rate of admitting patients or the referral pattern. The diagnostic criteria for IMS was different for the two time periods, with the inclusion of cognitive testing for the second group only. If identical criteria had been used, perhaps the incidence of IMS would have decreased rather than remained the same from the earlier to the later time period; this would then be a possible explanation for the decreased incidence of agitated IMS. Retrospective studies have known weaknesses pertaining to the completeness, accuracy and interpretation of the recorded information. The definitions of IMS and agitated IMS required consideration of several criteria. The assumption that recording practices pertaining to these criteria did not change appreciably between the two time periods, even though three new management practices were initiated, is questionable.

In Musgrave's study, data were collected prospectively on a daily basis, but only cross-sectional data collected just before death were reported. The reasons for this restriction were not given. Five patients were excluded because they lived longer than ten days from entry to the study. This was not explained and is baffling, given that the data presented for the other subjects were from 24 to 48 hours before death.

2.2.6 Conclusions

These six studies represent all of the identified, clinically-based, published studies on this topic. Given their limitations, it is difficult to draw any firm conclusions which would impact on clinical care. The benefit-to-harm trade-off from fluid therapy is uncertain. As others have recommended, the only recourse available at this point in time is to assess each patient's individual circumstances, including the patient's and family's wishes, in order to formulate recommendations regarding fluid therapy for that patient. The ethical and legal aspects of this issue may become clearer if evidence to clarify the clinical aspects can be obtained through more rigorous research.

Thirst and dry mouth appear to be common in dying patients, and may be troublesome in certain subgroups. Fluid volume deficits are probably also common as death approaches. Further research is needed using more rigorous designs to test hypotheses pertaining to the effects of fluid deficiency and fluid therapy on mental status, thirst, and dry mouth. Other outcome measures may be important as well, but need to be identified through further clinical studies, preferably, at least, prospective cohort studies. Surveys of clinicians, researchers, patients and families would be another means of determining relevant outcome measures. Consensus methods, such as the Delphi method, may be helpful here⁹³. Outcome measures considered should include measures of QOL which incorporate psychological, social and spiritual aspects of the person and family in addition to physical symptoms⁹⁴.

The subpopulation of the terminally ill to whom the controversy regarding fluid therapy applies is poorly understood - some authors appear to emphasize the immediate pre-death period as being the relevant time, while others consider patients at an earlier stage. There may be groups for whom agreement is good, with respect to the overall benefits and harms of providing or not providing fluids, and

another group for whom true controversy and uncertainty exists. The latter group should be considered the subjects of more rigorous trials, such as RCTs⁹⁵. Discussions with interested parties, clinicians, researchers, patients and families, may help to clarify this issue, perhaps using the Delphi method.

Some questions which deserve further research are:

- (1) What are the etiologies of thirst and dry mouth? How are they related? Would maintaining optimum physiologic fluid status impact on these symptoms at all? Does mouth care alone truly suffice to control these symptoms? What other factors are relevant?
- (2) What impact does fluid status have on mental status near death? Would artificial fluid therapy affect the incidence and severity of cognitive impairment in the dying? For what population of patients does uncertainty exist with respect to the use of fluid therapy for this indication?
- (3) What other outcomes are pertinent to adequately investigating the effects of fluid status or fluid therapy on the dying? For what population are these outcomes relevant?
- (4) What is "normal fluid status" in the dying? How is this reflected in clinical and laboratory measures and how are these affected by changes in fluid status?

In Chapter 3 a study of the effects of fluid status and fluid therapy on the dying is presented. The limitations of the small group of studies identified in this review raise questions about the challenges faced in doing palliative care clinical research. This is discussed in the next section of this background chapter, using the six studies from this review as illustrations, before presenting the clinical trial.

2.3 OBSTACLES TO PALLIATIVE CARE CLINICAL RESEARCH

2.3.1 Introduction

Systematic reviews have several purposes. Jenicek proposed the following list of objectives: "to confirm information (hypothesis, proof, initial findings); to find errors; to search for additional findings; and to develop new ideas (hypotheses) for further research and future original studies."⁷⁶ Thus, beyond systematic reviews' recognized primary purpose of providing answers to clinical questions, they are also used to direct future research. This is usually by helping develop new hypotheses, but a secondary objective may be to reveal methodological issues or obstacles which require consideration. The development of hypotheses was considered in the previous section; obstacles are considered here. Further exploration of palliative care research obstacles is presented in Chapter 4.

The systematic review in the previous section identified six recently published studies exploring the effects of fluid volume status or fluid therapy on the dying. These studies were noted to have the following characteristics:

- (1) they were all descriptive rather than analytic in design;
 - (2) they almost all had relatively small sample sizes;
 - (3) they were all potentially biased; and
 - (4) they were all limited with respect to generalizability.
- Are these relatively common features of palliative care clinically-based studies? If so, why? Are stronger designs used very often? Why have so few studies been performed on this topic? Do palliative care clinical researchers face obstacles which are particularly important to this field?

2.3.2 Development of a Young Science

Palliative care is a young discipline. Its modern era began in 1967 when Dame Cicely Saunders opened St. Christopher's Hospice near London, England. This free-standing hospice, physically and financially separate from the

hospital system in place at the time, was established to provide specialized care for terminally ill patients, who were perceived to be receiving inappropriate or inadequate care within the traditional health care system⁹⁷. But, St. Christopher's pioneering effort went beyond solely providing dedicated care for the dying - such establishments had existed since the end of the last century. It included, for the first time, education and research as equally important components of the hospice mandate⁹⁸. By doing so, it not only acquired international renown, but was able to spread the hospice or palliative care philosophy throughout the United Kingdom and to other countries and to spur the development of palliative care programs around the world⁹⁹.

In Canada, the first palliative care programs were created in late 1974 at the St. Boniface Hospital in Winnipeg and in January, 1975 at the Royal Victoria Hospital in Montreal. From this beginning, palliative care services spread across Canada and there are now several university-based, academically oriented programs¹⁰⁰. In the United States, the first service opened in 1974, but major expansion only occurred during the last decade¹⁰¹. Australia, New Zealand and several countries in Europe now have well developed programs as well¹⁰². Many countries have created national palliative care organizations.

Palliative medicine was recognized as a medical specialty in the United Kingdom in 1987 and soon after that the same occurred in Australia. In the last 12 years several palliative care specialty journals were inaugurated in different countries, providing a wider forum for publication of palliative care related articles and studies. Regional, national and international conferences have occurred and meetings focused on palliative care research have been held as well. Although the hospice movement was born outside of the traditional health care system, its development had brought it back into the mainstream¹⁰³.

Despite the early interest in research and the overall advances experienced by palliative care, research lagged behind¹⁰⁴. This was a target of criticism for several years. In 1981 Torrens wrote:

When one looks for hard data, well-controlled studies of a more scientific nature, objective measures of outcome on hospice programmes, one finds that the facts are not available. With the exception of a few major studies carried out by people like Robert Twycross, John Hinton, Colin Murray Parkes, one simply does not find the wealth of objective evidence that really should be there¹⁰⁵.

In 1985, Gotay stated:

Much of the early writing about hospice programs tended to be descriptive and anecdotal accounts of a single program with very small numbers of subjects...many current studies are paying more attention to methodological issues that may lead to results that can be interpreted more critically and can be generalized to other programs¹⁰⁶.

The impression that much of palliative care was based on anecdote, opinion and tradition has been repeated by others since then^{107, 108, 109}.

Ahmedzai believed that the great strides made by palliative care over the past three decades were mainly attributable to educational endeavours, but that a realization occurred in the 1980s that palliative care "had to prove its worth more rigorously, by means of published research". When addressing the area of clinical research, he said, "there has been in the past a tendency to dwell on empirical observations (particularly by means of single-center surveys or retrospective series), rather than on prospective and controlled trial designs."¹¹⁰ One notable exception was research in pain management¹¹¹, which MacDonald believed was highly successful because of the collaboration of basic scientists, neurobiologists and clinicians¹¹². Bruera felt that because palliative care programs developed largely outside of academic centres, their main focus was on clinical

care and education, but that a greater awareness of the need for research had evolved with the discipline¹¹³. Twycross reported in 1993 that the volume of research appeared to be growing, noting a 1990 survey which showed that over 100 centres were involved in palliative care research in Europe¹¹⁴.

Recently criticism has been levelled at the apparent lack of proper testing of one of the foundations of cancer pain control, the "three-step analgesic ladder" promoted by the World Health Organization (WHO) since 1986¹¹⁵. A systematic review of studies evaluating the effectiveness of this approach was performed by Jadad and Browman. They identified fourteen papers, all labelled as case series, four of which were retrospective. (The authors used the following definition for case series: "Case series are studies in which events in one or more patients are described with no reference to a control group".) Eight studies met the eligibility criteria for the review and several additional methodological flaws were identified in these studies. Some of these flaws were: short or variable follow-up periods; small sample sizes; and high rates of exclusions and dropouts. The reviewers concluded that these studies provided valuable information regarding cancer pain, its treatment and its course, but that the effectiveness of the WHO analgesic ladder for managing cancer pain was not demonstrated using the methodologies employed. They went further to recommend that it would be inappropriate to design policies based on the evidence available to date, and that controlled trials were needed.¹¹⁶

A letter from palliative care physicians in response to this review included the statement, "In our opinion, the contribution of Jadad and Browman is not constructive and is more likely to impede progress than to help" and they noted that the effectiveness of the analgesic ladder was obvious to clinicians working in the field¹¹⁷. Despite concerns, there

was agreement by authors of a second letter that some randomized controlled trials were needed¹¹⁸.

2.3.3 Issues in Palliative Care Clinical Research

In 1991 the Expert Panel on Palliative Care made recommendations to the Cancer 2000 Task Force concerning palliative care for cancer patients in Canada and the future development of the field with respect to service, education and research¹¹⁹. In their report they acknowledged that clinical research was difficult to do when patients were near death. They specifically noted the following issues which have impacted on the conduct of palliative care clinical research:

- (1) they stated that ethical and medical reasons made it difficult "to control variables over a prolonged period of time especially because of the instability of this population";
- (2) they noted problems with heterogeneity in the study population;
- (3) the need for access by palliative care researchers to clinical settings with an adequate flow of patients was emphasized;
- (4) the fact that most clinicians in palliative care lacked research training and easy access to research expertise was pointed out; and
- (5) funding for research in palliative care was reported to be inadequate.

All clinical researchers face obstacles while trying to conduct studies in their field of interest. Some important obstacles to palliative care research may be of particular relevance to this field because of its unique clinical setting as defined by the patients, the goals of care, the professional carers involved and its historical development. The Expert Panel highlighted some issues which could be included in this group of relevant obstacles, but there are

others.

The funding issue was a major aspect of the Expert Panel's report; funding for palliative care research from the major research granting bodies was found to be almost nonexistent. The lack of support from 'the cancer establishment' was seen as one main reason why palliative care research had not progressed, while the research which occurred was primarily with pharmaceutical companies or by virtue of small local research grants, private donations or the diversion of operating funds. Based on their experience palliative care researchers believed that grant applications to major cancer research funding agencies were futile - criticism and rejection by reviewers was perceived to be due to their lack of knowledge of the field and their opinion that palliative care was a low priority research area¹²⁰.

The belief that palliative care research was poorly funded relative to other areas of clinical research such as oncology has been mentioned by several researchers and commentators in the field^{121, 122, 123, 124}. In the United Kingdom much of the research funding has come from cancer charities¹²⁵. Bruera recommended two methods to increase funding: include in the granting agencies persons who understand and can promote this type of research; or create separate granting agencies for palliative care research¹²⁶.

The lack of both trained palliative care researchers and access to research expertise has been noted elsewhere^{127, 128}. The Expert Panel recommended the establishment in Canada of research fellowships for trainees from medicine, nursing or other disciplines interested in a career in palliative care research. Proposals for increased research training opportunities have been made in the United Kingdom^{129, 130}. MacDonald saw the general lack of association with academic units and the lack of academic recognition as major barriers to research in this area¹³¹. He also felt that increased linkages with cancer centres, given their resources, would

benefit palliative care clinical research¹³².

In a discussion of palliative care research in the Oxford Textbook of Palliative Medicine, Calman and Hanks pointed out that negative attitudes towards research with the terminally ill have been a deterrent to scientific inquiry. They stated:

Indeed there is a view that scientifically rigorous clinical research is incompatible with the basic tenets of palliative care, and the emotive accusation of experimenting on the dying has been an ever-present deterrent to some.

They cited two reasons that have been given to dissuade clinical research in this area: one, that the patients were too ill and vulnerable; and two, that there was not much more to be learned¹³³. Some palliative care workers believed that research competed with patient care¹³⁴ and was contributing to the 'medicalization' of palliative care, threatening the essence of the care that had existed¹³⁵. Thorpe and Ahmedzai felt that the major problem interfering with research was the clinical staff's wish to protect their patients^{136,137}, even though Thorpe observed that most patients were interested in taking part in research projects.

Ethical issues arise whenever the propriety of including the dying in clinical research is considered. De Raeye wrote what she acknowledged to be a provocative article in which she questioned whether research with the dying should be done at all. She cited their poor emotional and physical state and their vulnerability as reasons to refrain from asking their participation. She felt that dying patients' freedom to choose, either to participate or to withdraw, was potentially compromised because of their poor condition, place of care and position of dependency. Role confusion, in which an investigator's relationship with the patient was interpreted by the patient to be one of a friend, nurse or therapist rather than researcher, was seen as a possibility that could add to their vulnerability. The potential that questions asked could provoke distress in some patients was a concern as

well¹³⁸.

In response to this article, a group of palliative care researchers argued that the competent dying retained autonomous decision-making capabilities and should be given the opportunity to participate in research as a means of "participating in society, giving to others or finding purpose and meaning". They also argued that the ethical concerns raised by de Raeye were relevant to all clinical research, not just research with the dying¹³⁹.

The vulnerability of this population has been generally recognized^{140,141}. Calman and Hanks suggested that researchers needed to be cautious and not take advantage of the patient's situation; they recommended that a family member always be involved when a patient is approached for participation in a study¹⁴².

Kristjanson et al. reviewed a sample of 55 studies published over eight years in four palliative care journals to explore to what extent ethical principles were addressed by palliative care researchers¹⁴³. They believed that the palliative care population was very vulnerable and that the subjects in the studies reviewed possibly lacked total freedom to refuse to take part due to their need for clinical care - often the caregivers were also the researchers. Their poor general status may have interfered with the informed consent process and their ability to withdraw may have been compromised by their rapid deterioration. They did feel that the dying had a right to decide about participation in research, but that the burden imposed must be limited to a 'slight degree' only. Possible risks or burdens which they identified included: invasion of privacy; the personal nature of questions; the burden of participation; and side effects of interventions. The burden of participation included the number, complexity, frequency and duration of outcomes assessed. Some studies dealt with these problems by using brief, multiple choice questionnaires, using unstructured or

retrospective interviews or hiring of data collectors with special clinical and counselling skills. They also reported that the reviewed articles occasionally provided information supporting the impression that at least some patients derived benefits from participation in research. Some of those involved in interview-type studies may have obtained a therapeutic effect, some patients possibly achieved better symptom control, and some may have benefited by simply feeling hopeful that they had helped others.

The belief that many dying patients do derive direct benefits from being involved in research is often stated anecdotally and used to support research in this area, countering some of the ethical and attitudinal concerns¹⁴⁴. There has been more direct evidence to support this. Davies et al., reported on the challenges they faced in conducting a qualitative study in palliative care¹⁴⁵. At the end of each interview they asked the interviewees what the experience had been like for them. Responses indicated that all family members, including the patients, found the interview to be of benefit in several ways: one patient stated that it helped to get things out into the open; a family member believed that it was useful to put into words what was thought and felt; and others reported that the interview was difficult, but that they perceived some value anyhow. Some reports of quality of life studies have included the benefits that were experienced by the terminally ill subjects involved. The opportunity to discuss important topics which had been difficult to raise previously¹⁴⁶ and the chance to confront issues which were previously ignored¹⁴⁷ were examples reported.

There have also been ethical concerns regarding design issues. These have involved the use of randomization^{148, 149, 150} and control groups, especially if placebo controls were used¹⁵¹. Similarly, the use of 'invasive' tests such as blood tests have been questioned on ethical grounds¹⁵². No explanations for the ethical basis of

these concerns were given.

The occurrence of cognitive impairment in the terminally ill cancer population has been shown to be high in several studies: Massie et al. followed 13 hospitalized, terminally ill, cancer patients until death and 11 (85%) developed delirium¹⁵³; Bruera et al. retrospectively reviewed 30 consecutive terminal cancer patients who died in hospital after an admission of one week or more and found that 23 (77%) had developed delirium or severe sedation (excluding those that developed symptoms in the last 48 hours of life)¹⁵⁴; and Bruera et al. followed 47 terminal cancer patients who died in a PCU out of which 39 (83%) developed 'cognitive failure'¹⁵⁵.

This high incidence of cognitive problems has several potential effects on research with the dying, one of the most important being the effect on the informed consent process. Calman and Hanks maintained that patients with obvious confusion or with doubtful ability to understand should be excluded from research¹⁵⁶. Bruera concurred and recommended that all patients be screened for cognitive impairment and excluded from clinical trials if impairment was present. He saw this as important from an ethical point of view, but also methodologically since impaired subjects were more likely to be unable to complete a trial. He stated that the only exception to this recommendation would be if the research dealt with the management of delirium in terminal illness¹⁵⁷. Kristjanson et al. raised the possibility of using a proxy to consent on behalf of an incompetent patient. They suggested that this could occur if the patient had designated a family member proxy decision-maker prior to deteriorating¹⁵⁸. On the other hand, guidelines developed in the United Kingdom, dealing specifically with research in palliative care, stated:

Consent must be given by the patient; it is important to encourage patients to discuss their participation with their relatives and/or carers preferably in the presence of one of the researchers¹⁵⁹.

There has been a lack of consensus on a clear definition for the palliative care patient population, both for clinical and research purposes. Gotay raised the question of definition regarding life expectancy, extent of disease and diagnoses other than cancer¹⁵⁰. Twycross and Dunn asked, "...what is the definition of dying and when does it begin?"¹⁵¹ MacDonald argued for a widening of the time-frame in which palliative care research, especially symptom control research, should occur¹⁵²; others disagreed with involvement at earlier stages of disease.¹⁵³ Doyle argued that the definition used for palliative medicine when it became a specialty in the United Kingdom should apply:

The study and management of patients with active, progressive, far-advanced disease for whom the prognosis is limited and the focus of care is the quality of life.

According to Doyle this did not limit care to any pathology or time-frame, but did exclude chronic conditions which were not imminently life-threatening¹⁵⁴.

However defined, the population studied has been heterogeneous, which carried repercussions for the research. Max and Portenoy in their discussion of pain research in palliative care noted that there were many patient characteristics which could affect the results of a trial: demographics; psychological factors; historical factors (chronic pain, substance abuse, psychiatric history); type and extent of cancer; previous and ongoing anti-cancer treatments; presence of other diseases; presence and severity of other symptoms; use of other treatments; pain characteristics; mechanisms of pain; and prior pain therapy. They discussed handling this by defining a narrower population which would potentially decrease the variance in the outcome measures and facilitate the drawing of conclusions. The trade-off would be slower recruitment and decreased generalizability¹⁵⁵. Another approach suggested was to stratify by important characteristics before randomization, although this would

increase the complexity and size of the trial. The development of a staging system for cancer pain was recommended as a means of decreasing the number of necessary strata¹⁶⁶. The population heterogeneity reported in pain studies could be extended to other types of research in palliative care.

Many clinical trials have required the exclusion of patients with severe or unstable disease or complications, resulting in the exclusion of a large proportion of palliative care patients and decreased generalizability. Kerr suggested adjusting the exclusion criteria to make the study populations more representative of the target population.¹⁶⁷

Bruera reported that his group had found that 80% to 90% of patients approached for participation in studies agreed to take part¹⁶⁸. A group from the United Kingdom had a different experience - out of 235 eligible patients referred over a 12 month period for consideration for entry into one of ten different palliative care trials, only 142 (60%) consented¹⁶⁹. In another situation, a research nurse reported working for four months to recruit patients to two studies. She accessed 30 patients; five were excluded because they were too ill, one was ineligible and only two declined. Patient consent was not a problem in this case, but access to patients was¹⁷⁰.

Three studies are reviewed next based on articles written by the authors summarizing issues they faced during the design and execution of their projects.

The paper by Davies et al. reviewed other aspects of their experience¹⁷¹. Measurement of outcome measures was a major concern in their project, which aimed to understand the experiences of patients and families receiving palliative care services. They considered using multiple outcomes, but decided that asking families to complete so many was inappropriate. Individual scales were thought not to be applicable to the situation because they had been developed

and tested in other populations using different theoretical frameworks. They wanted to assess the families' whole experience rather than one component only, which led them to choose a qualitative research design.

Interviews were conducted with the family as a group (the patient, spouse and one child over 18) and with individual members. Recruiting families for such a study at a difficult time was a challenge - the group interview prevented the participation of some families. The staff members of the agencies involved were hesitant to help in the recruitment. They were concerned with patients being in their terminal stage, being too uncomfortable, sleeping much of the time or having been "through enough". The impression was that the patients and families were being protected by the staff. A research team member became actively involved in reviewing patients with staff members in order to improve recruitment.

There were other obstacles to recruitment as well. Families declined participation for several reasons: they wanted to protect the patient; they had taken part in studies previously; or they had been "through too much". Sometimes after successful recruitment the patient became too ill to participate or died before the interview occurred.

Potential risks to families were identified, including emotional discomfort, anxiety and the revelation of intimate secrets. They also recognized that they were asking families, already under much stress, to spend time taking part in a study when they had so little time left to spend with the patient. Challenges faced during interviews included the conflict between stopping early because of patient discomfort and the need to obtain complete data. Concerns regarding role confusion also arose.

The second study, the National Hospice Study (NHS), was a major non-randomized, comparative study carried out in the United States in the early 1980s in which the care of terminal cancer patients in hospice (palliative care) and non-hospice

settings were compared¹⁷². Forty hospices and 14 conventional oncological care settings were selected and 1754 patients (1457 hospice and 297 non-hospice) were included. The rate of refusal of participation in the hospice settings was 3.4%¹⁷³ while in the conventional care settings it was 20.6%. The dropout rate after consenting was 4.4% in both settings. Interviews with the patient and the primary care person (PCP) were conducted at study entry, seven days later, then every 14 days until death. Only patients who died during the study were analyzed because analysis occurred relative to the date of death.¹⁷⁴

Mor discussed issues related to measuring outcome measures in palliative care, using the data from the 1457 hospice patients to illustrate¹⁷⁵. Several patient outcome measures were commonly reported by the PCP because most patients could not be interviewed close to death (although PCPs were not used to determine the patients' mood state). Mor acknowledged that even the use of a family member as a proxy informant for a patient could be biased, but felt that the PCP knew the patient best, compared to staff members or independent observers. Despite the potential lack of accuracy with respect to the patient's experience at a point in time, he argued that changes in the PCP's view over time may be valid. The use of the PCP as proxy reporter for the patient was also in line with the palliative care philosophy of including the family with the patient as a unit of care. They found that patients' and PCPs' assessments of the patients' pain and other symptoms were moderately correlated.

The use of proxy scoring is controversial. Cassileth felt that a family member's rating of the patient's pain or psychological status was "so confounded that it should be avoided"¹⁷⁶. Mount and Scott questioned whether the assessment of the QOL of the patient by the primary care person in the NHS was valid¹⁷⁷. Studies have shown that doctors' assessments of patients' QOL correlated poorly with

the patients' and showed marked variability between doctors¹⁷⁶. In another study, good correlations between 28 patients and their PCPs were found for some, but not all, items in a questionnaire about the patients' experiences in the month prior to admission to an inpatient hospice.¹⁷⁷ Agreement was good for items pertaining to activities of daily living, physical symptoms and the evaluation of care received. More disagreements were noted for psychological symptoms, the degree of symptom distress and the main symptoms experienced at the time of admission. Epstein et al.'s study compared the responses of community dwelling elders and their lay proxies with respect to the subjects' health status and health care satisfaction. They concluded by advising not to mix proxy and subject responses when examining the health status of patients - although responses correlated, the proxies scored emotional health and satisfaction lower than the patients did. Of interest, proxies who spent more time helping the subject rated the subjects's functional status and social activity poorer than did the subject and subjects with poorer health tended to rate their health lower than did the proxy¹⁸⁰.

The National Hospice Study found that the patients' conditions were of major importance to the conduct of the study. The last interviews occurred an average of seven days before death¹⁸¹ and the second-last set of measures were collected about 21 days before death. The investigators found that patients who died quickly (within days) after admission to a hospice program were underrepresented in the study sample, and may have comprised up 10% of the palliative care population. Of the sample of hospice patients, only 35.8% were able to answer questions about pain severity at the last interview before death, a decrease from 61% at the next-to-last interview. This decrease was partly due to deterioration in physical symptoms and partly due to worsening cognitive impairment. Twenty per cent of patients were unconscious, confused or 'completely incapacitated' in the last week of

life and only 35% were thought to have their normal cognitive function.

Prospectively after the first interview rapid attrition occurred in the sample size of hospice patients; the main reason for attrition was death. Twenty per cent had only one interview and 40% had no more than two. Aggravating the diminishing sample size was the fact that only about half of those alive at each interview could respond to psychosocial self-report items. The non-responders were much sicker than responders, as assessed by performance status, symptom frequency, level of awareness and other symptoms. The high rate of attrition and non-response was noted to be a potential cause of bias since the population able to complete self-reported measures would not have reflected the population of all hospice patients.

Mor also discussed the need to select scales which have been tested in the specific population of interest; otherwise misleading results could be obtained. As an example, he mentioned the use of depression scales which emphasize somatic symptoms; these may overestimate the prevalence of depression in the terminally ill¹⁸². Others have commented on the lack of relevant outcome measures for use in palliative care research. Mount and Scott, in a critique of the National Hospice Study, wrote that measures assessing the impact of palliative care would have to measure:

... an increased sense of personhood and an enhanced context of meaning, improved communication within the family and between family members and health care workers, lessened uncertainty and fear of the unknown, greater acceptance of the reality facing them, greater ability to express fears, doubts, guilts and anger, and the significance of being able to pray together ...¹⁸³.

Johnston and Abraham noted that outcome measures have been slow to develop for palliative care and they surmised that this may have been due to difficulties in assessing the "unique needs of the dying" or because of ethical and physical

problems that arose¹⁸⁴. They wondered whether the measures needed to change as the disease progressed. They reported on several instruments which have been developed recently and suggested that qualitative research methodologies be used to validate quantitative measures. A working party in the United Kingdom also compiled a list of outcome measures used or suggested for use in palliative care¹⁸⁵.

The third study, by McWhinney et al., reported on the difficulties they experienced in trying to carry out a randomized controlled trial to evaluate a palliative care home support team, which had already existed for 18 months¹⁸⁶. The eligibility criteria required the adult patient: to have advanced cancer; to be cared for at home by an eligible caregiver and to have an expected survival of two months. Comparisons were between a control group of patients put on a one month 'waiting list' and a group given immediate assessment by the team. Data collection occurred at baseline then at one and two months, with one month being the main comparison point. Outcome measures assessed included pain, nausea, quality of life and caregiver's health. Their sample size goal, based on an appropriate calculation, was 110 subjects per group, allowing for a 20% attrition rate.

Within three months the following problems had arisen: the average monthly intake for the study was below expectation, despite efforts to attract referrals; the proportion of subjects who died before the one month follow-up point was greater than expected; some patients were not entered because of a predicted early death, but were later found to be eligible; some control group patients were admitted to the palliative care unit shortly after the baseline assessment, exposing them to a type of care which matched the home support team's care; and some patients and caregivers did not complete the one month follow-up assessments. The patients were failing to complete the one month assessments due to symptoms and cognitive impairment;

the caregivers' reasons were unclear, but, according to the authors, presumably were due to the "devastating and exhausting experience". By the end of the trial they had received 307 referrals (an average of 3.7 per week) out of which 141 were ineligible and 20 refused or died before randomization. Of the 146 randomized, 53 were not evaluable at the one month follow-up - 36 died and 14 did not complete the questionnaires. Only 74 caregivers completed the one month questionnaires. (The numbers listed are as given in the original article.) There were no statistically significant differences between the two groups.

The authors felt there was an ethical problem with the randomization process which may have affected the success of the trial - they believed that equipoise was not present between the two interventions being compared. They questioned whether palliative care services could be evaluated using randomized trial methodology and recommended using different methods in parallel instead. They thought that trained interviewers would have increased the response rate and the quality of the data at one month.

2.3.4 The Systematic Review Studies as Illustrations

The six studies identified in the systematic review present a further illustration of issues affecting palliative care clinical research. All were very recent studies on an important topic of wide relevance. The fact that they were all recent publications may reflect changes that have occurred in attitudes towards clinical research with dying patients, especially on sensitive topics. Despite this possibility, none of the studies used an experimental design. Reasons for choosing the design were not given by most of the authors, although there may have been concerns about allocating patients to intervention groups. Waller stated that there were "ethical limitations on conducting clinical trials with patients in the last days of life". This reluctance may have

stemmed partially from strongly held opinions regarding the effectiveness or dangers of an intervention. Ellershaw stated that the subjects in his study "died without artificial fluid therapy, according to normal hospice practice" and Waller clearly pointed out that his hospice's "policy is to avoid intravenous therapy whenever possible". The reasons that thirteen patients received IV fluids in Waller's study were outlined by the authors - several were transferred with an IV in place and others had IVs started at their families' request. If indeed there were attitudinal or ethical concerns regarding allocation to comparison groups, this would have been an obstacle to performing high quality comparative trials, and especially randomized controlled trials.

Most of the studies had small samples, the reasons for which were not always clear. All six included subjects solely from one or two inpatient units or hospices; none of the authors elaborated on their choice of sampling frame. This may have been a choice of convenience or possibly there were problems identifying or accessing palliative care patients at other sites. It may be easier to define a population within the confines of a unit or hospice than to try to define a wider population receiving care at multiple sites, including throughout the community.

The proportion of potential subjects excluded was important in several studies, although this information was not always provided. This appeared to be more important than the proportion of eligible patients who declined to participate. Exclusions were largely due to impaired mental status. In Burge's study, out of 123 patients considered, 66 (54%) were excluded. Over half (53%) of these were because of mental status problems (confusion, decreased level of consciousness, agitation, anxiety), another 26% were due to physical weakness and 8% because of death. Only 5 patients refused to participate. He demonstrated that the group of excluded patients differed significantly from the study sample

with respect to survival, fluid intake, and mouth care needs. In McCann's study, after one year only 48 consecutive patients were considered out of which 16 (33%) were excluded, presumably because of impaired mental status. Refusals were not mentioned. Musgrave considered 38 patients and excluded 19 of these. Eleven of the 19 exclusions were because of decreased level of consciousness. She did not enumerate the number of refusals.

Cognitive function and competence were relevant to the informed consent process. Ellershaw allowed for consent to be given by a relative on behalf of a patient who was unable to do so. Burge required all included subjects to be able to give consent on their own and he excluded those who were incapable of understanding and deciding. Musgrave required patients to approve their participation verbally.

Ellershaw found a different problem related to the high prevalence of mental status impairment in the terminally ill - only 23 of 82 subjects (28%) could respond to questions pertaining to subjective symptom experiences. In McCann's study, the use of proxy assessment by a joint effort of the patient's family and the team was included in the protocol for assessing the level of comfort of patients who lost consciousness. He did not indicate the frequency with which this was needed.

Other ethical concerns were mentioned in these papers. Without giving details or references, Burge stated that there were "ethical and comfort concerns of using accurate but invasive methodology" for measuring fluid status. In Musgrave's study laboratory data were available on only twelve of the 19 subjects (63%). The availability of this data required that laboratory work be a necessary part of the patient's care and not specially ordered for the study alone. Her study was carried out without research ethics board approval because it "neither affected patient treatment nor involved any invasive procedures". It was not clear whether

there was an ethical concern about approaching dying patients for consent to participate in a study involving venipuncture. Such a concern, however well-founded, would be an obstacle to the planning of research in palliative care.

In Burge's study population heterogeneity was particularly noticable when survival was considered - within the study population there were patients who died less than two weeks after the study and others who survived for several months. A similar type of heterogeneity was present in McCann's paper.

Other obstacles noted in these studies included Burge's note that the clinical assessment of dehydration was difficult due to the clinical effects of malignancy, although he gave no further details. McCann found the "comfort" of patients difficult to grade and called for a more objective measure of this. McCann and Ellershaw both noted problems associated with competing interventions such as opioid use.

None of the six studies acknowledged any source of external funding specifically for the study reported. Burge reported personal support in the form of a fellowship.

2.3.5 Summary

Palliative care is a young and developing clinical field in which progress in research has lagged behind other advances. Much of the research done has been uncontrolled and descriptive in nature.

Although palliative care researchers are not unique in having barriers to face when attempting to do clinical research, there may be some obstacles which are particularly relevant to this field. These must be recognized and considered when planning specific studies and overall research agendas.

Obstacles which were identified included the following:

- (1) negative attitudes towards research with the dying;
- (2) ethical concerns about the vulnerable population, burdens

on patients and families, use of comparison groups, randomization, use of investigations and informed consent;

- (3) lack of consensus on a definition for the palliative care population, especially regarding stage, extent of disease or prognosis;
- (4) the use of eligibility criteria which usually exclude patients with severe disease, lessening generalizability;
- (5) population heterogeneity involving multiple factors;
- (6) limited access to palliative care patients for recruitment;
- (7) the high prevalence and incidence of cognitive impairment in the population, affecting recruitment, consent and data collection;
- (8) the unstable population, resulting in losses to follow-up and missing data;
- (9) the lack of relevant palliative care outcome measures;
- (10) the common use of multiple and changing treatments due to changes in the patients' conditions;
- (11) the lack of training and access to research expertise;
- (12) the lack of adequate funding for research.

The state of knowledge which exists pertaining to the effects of fluid status and fluid therapy on the dying has been reviewed and questions proposed for further research. Obstacles which have affected research on this topic specifically and in palliative care in general have been identified. The next chapter presents a study that explored the effects of fluid status and fluid therapy on the dying. A further examination of obstacles to palliative care research is presented in Chapter 4.

CHAPTER 3

A STUDY OF THE FLUID VOLUME STATUS OF CANCER PATIENTS ADMITTED TO TWO PALLIATIVE CARE UNITS (Fluid Status Study)

3.1 SYNOPSIS

As discussed in Chapter 2, controversy prevails regarding the effects of fluid volume deficiency on the dying and whether artificial fluid therapy provides overall benefit or harm. Clinical practice varies and is largely based on experience, opinion, anecdote and extrapolation from other populations and animal studies. Relevant clinical research involving terminally ill patients has consisted essentially of a few uncontrolled, descriptive studies. There is a lack of consensus regarding the important outcomes which need to be considered and the population for whom the therapy is most uncertain. The situation is complicated by the prominence of psychological, social, spiritual, ethical and legal aspects to the issues.

In this chapter, an exploratory study utilizing an experimental, nonrandomized, comparative design is reported. Its goal was to examine multiple clinical outcomes potentially affected by fluid status and fluid therapy in dying patients. Two groups of 33 terminally ill cancer patients at risk of fluid deficit were assembled, each in a different palliative care unit. One group received parenteral fluid therapy while the other did not. Fluid volume status was assessed regularly using selected aspects of the clinical examination, biochemical measures and fluid intake and output measurements. Multiple symptom-related outcomes potentially affected by fluid status or fluid therapy were monitored serially. Medications used by the patients were recorded daily.

The experimental and study populations were found to differ with respect to some baseline demographic measures. The study samples were also noted to exhibit difference with

respect to several important outcome measures at the start of the study. Because of this, a post-hoc secondary analysis was carried out using the day of death, rather than the day of study entry, as the common point in time. Both the primary and secondary analyses are presented.

The study's limitations are reviewed and implications of the results for practice and research discussed. Obstacles faced during the planning and execution of the trial are reviewed as well. Recommendations pertaining to subsequent research on this topic are presented.

3.2 GOALS AND OBJECTIVES

This was an experimental, nonrandomized, open, comparative study conducted in two PCUs, one at the Edmonton General Hospital in Edmonton, Alberta and the other at the Bruyère Pavilion (formerly the Elisabeth-Bruyère Health Centre) of the Sisters of Charity of Ottawa Hospital in Ottawa, Ontario. It was planned as an exploratory study whose goal was to generate hypotheses regarding the effects of fluid status and fluid therapy on the dying. Specific objectives were:

- (1) to identify symptoms in the dying which may be affected by fluid status and fluid therapy; and
- (2) to identify physical signs, fluid intake and output measures and laboratory studies which may indicate the fluid volume status of the dying.

The protocol was approved by the research ethics boards of both hospitals. The study was not externally funded, nor was external funding sought.

3.3 METHODS

3.3.1 Subjects

Basic criteria required before a patient could be considered for this study were that the patient:

- (1) be an inpatient in either PCU participating in the study;

- (2) be able to understand and speak English in Edmonton and either English or French in Ottawa;
- (3) have a diagnosis of advanced cancer; and
- (4) not be aphasic.

No age limits for inclusion were defined since both units admitted only adults or older adolescents. Table B.1 displays the characteristics of the two units with respect to annual statistics and admission criteria at the time of the study³⁷ (personal communications). This experimental population was used for the following reasons:

- (1) the inpatient populations of the two units provided an easily accessible and definable source of participants for the study;
- (2) the two units' opposite approaches to fluid therapy allowed for two comparison groups to be assembled without requiring any other form of allocation to experimental groups (ethical concerns existed at both sites regarding randomized allocation);
- (3) the management practices of the two units could be easily assessed and compared;
- (4) the study was not directly funded and lacked resources for a wider sampling frame;
- (5) resources for translation beyond the English and French languages were not predictably available at both sites and the need was anticipated to be small; and
- (6) aphasic patients could not be reliably assessed for competence to give consent, nor could they reliably provide subjective outcome information.

The study was limited to patients with cancer because the unit in Edmonton admitted only patients with this terminal illness. The target population was believed to consist of adult, advanced cancer patients admitted to palliative care units.

All consecutively admitted patients meeting the basic criteria had demographic information recorded which included sex, age, primary and metastatic tumour sites, other

diagnoses, pain stage according to the Edmonton staging system for cancer pain¹⁸⁸, the presence or absence of dysphagia and estimated weight loss over the previous six months. The latter two items were included because of their possible prognostic significance¹⁸⁹. The Edmonton staging system for cancer pain had been developed to predict the outcome of pain management in cancer patients. Patients were staged according to several prognostic factors into one of three stages: stage 1 - good prognosis for pain control; stage 2 - intermediate prognosis for pain control; and stage 3 - poor prognosis for pain control.

Prior to asking patients to consent to participate in the study, their competence to do so was assessed. This was a two step process with the first step involving the Folstein Mini-Mental State Examination (MMSE)¹⁹⁰ which is a brief, simple and reproducible screening test of cognitive function. Such formal testing of the cognitive function of advanced cancer patients prior to entry into a study has been recommended because impaired patients, not otherwise identified, may be incapable of giving true informed consent¹⁹¹. The minimum criterion for a determination of competency was a normal cognitive screening score of 24 or greater out of 30 on the MMSE (this cut-off point between impaired and normal cognition has been recommended previously and was shown to optimize sensitivity and specificity in a sample of hospitalized, general medical ward patients¹⁹²). If a patient was unable to do the full MMSE for physical reasons, it was scored out of a lower maximum score, based on the portions completed by the patient, and the cut-off point was lowered an equivalent amount (that is, six points below the maximum attainable score for the patient). The second step of the competence assessment occurred if a patient scored in the normal range, but subjectively appeared to be incompetent to give consent, according to the judgement of the assessor. Then, the patient was not approached for consent. If a

patient was judged to be incompetent at first assessment, either by a low MMSE score or by subjective assessment, but later improved to appear competent and to score appropriately on the MMSE, he or she was approached for consent at this later date.

When the study started, a person who was already an inpatient on one of the units was considered for the study if: the basic criteria for study entry were met; immediate discharge was not planned; the patient was not already fluid deficient clinically; and the patient was not receiving parenteral fluid therapy. If deemed eligible, such an inpatient had demographic information recorded and was screened for cognitive impairment/competency to determine whether he or she could be approached for consent.

Signed, informed consent was obtained from all subjects who agreed to participate. The information and consent forms were available in English in Edmonton and in both French and English in Ottawa.

3.3.2 Sample Size

No formal sample size calculation was done for this exploratory study. Prior to startup of the study, a goal of following a minimum of 30 to 40 patients in each group in the main part of the study (Phase II) was set, with the expectation that this could be achieved in about six to seven months.

3.3.3 Phase I and Phase II of Study

Figure B.1 shows a flow diagram of possible paths for patients considered for the study. Patients who consented entered Phase I, which was an observation period during which clinical monitoring occurred for evidence that the patient was at risk of developing or had developed a fluid deficit. If this occurred the patient entered Phase II, the main part of the study, unless exclusion criteria for Phase II were present

(see below). The goal was to place a Phase I patient into Phase II when he or she became at risk of developing a fluid deficit, but before a significant deficit had occurred. Phase I monitoring occurred through regular daily follow-up until the subject was discharged, died, or entered Phase II. No formal data collection occurred during Phase I.

A patient entered Phase II immediately after consenting to be in the study if he or she was at risk of developing a fluid deficit at that time or, if newly admitted to the unit, if he or she already had a fluid deficit. In Phase II, Edmonton patients, in addition to their usual care, received parenteral fluids by HDC, titrated to their needs, while Ottawa patients received their usual care with no parenteral fluid therapy. These approaches were consistent with the usual practices in the two units. Daily data collection occurred during Phase II.

3.3.4 Phase II Eligibility Criteria

A Phase I patient was defined as being at risk of developing a fluid deficit if a history of poor oral fluid intake, excess fluid loss, or both were present. Possible causes of poor fluid intake were anorexia, dysphagia, nausea, vomiting, bowel obstruction, decreased consciousness, or delirium. Possible causes of excess fluid loss were vomiting, upper gastrointestinal (GI) tract drainage, diarrhea, polyuria, sweating, and high fever, although other causes could be designated.

A patient was defined as having a fluid deficit if he or she met the definition for being at risk of developing a fluid deficit, and in addition had:

- (1) a history of decreased urine output, dry mouth sensation, thirst sensation, postural dizziness, or a combination of these; or
- (2) physical findings of a resting heart rate of over 100 beats per minute, a postural drop in systolic blood

pressure of 10 mm mercury or more on sitting, poor skin turgor assessed over the sternum, dry oral mucous membranes, enophthalmos, or a combination of these.

If fluid status or risk of developing a fluid deficit were uncertain, a twenty-four hour fluid intake and output measurement was performed prior to entering Phase II. In such a circumstance, a patient was defined as not being at risk of developing a fluid deficit if fluid intake was at least 500 mls. greater than the total measured output over 24 hours, allowing for insensible losses through the skin or expired air^{193,194}; a fluid deficit was defined as not present if the urine output was at least 400 mls per 24 hours, the definition used for oliguria¹⁹⁵. It was recognized that there were possible renal and post-renal explanations for oliguria, but patients undergoing this investigation at this time were doing so because of uncertainty regarding fluid status. All patients who did not have a 24 hour intake and output assessment prior to Phase II had it done as part of their Phase II outcome assessment. It was not required for all patients before Phase II entry because it may have delayed Phase II entry unnecessarily for many of the patients.

A Phase I patient was excluded from Phase II if the patient:

- (1) was receiving enteral tube feedings;
- (2) was in acute renal failure, evidenced by a rapid deterioration in renal function not due solely to a fluid deficit;
- (3) was in pulmonary edema; or
- (4) had a bleeding disorder (a possible contraindication to the use of hypodermoclysis¹⁹⁶).

Patients in Edmonton who refused hypodermoclysis or in Ottawa who received parenteral fluid therapy were excluded, and patients already in Phase II who altered their fluid therapy assignment were removed from Phase II at that time. Such excluded or removed patients could have entered Phase II later

if they met the criteria for entry at a subsequent time.

No new consent was required for patients to move from Phase I to Phase II since the original consent covered the study procedures in Phase II. Patients were free to withdraw from the study at any time. If a patient developed cognitive impairment, his or her family, usually involved in the original consent process, was free to withdraw the patient from the study.

Phase I patients meeting the inclusion criteria for Phase II had reasons for inclusion recorded. Also recorded were: the main route of fluid intake used most recently (oral, intravenous, subcutaneous or other); the reason for exclusion from Phase II (if pertinent); and the date of entry into or exclusion from Phase II. For patients entered in Phase II and withdrawn, the date and reason for leaving Phase II were recorded, with possible reasons being: death; discharge from unit; resolution of fluid deficit and risk of deficit for ten days (see explanation below); withdrawal of consent; and either premature discontinuation of parenteral fluid therapy for a patient in Edmonton or provision of parenteral fluids to a patient in Ottawa.

If a patient at some point in Phase II had no fluid deficit and was no longer at risk for developing a deficit, he or she was followed for a further ten days in Phase II, to confirm clinical stability with respect to fluid status. A patient in this situation in Edmonton did not receive parenteral fluid therapy during this ten day period. If the patient remained stable with respect to fluid status and risk of fluid deficit during this time, he or she left Phase II and re-entered Phase I at the end of the ten days. Patients could be considered for re-entry to Phase II later if their risk of developing a fluid deficit recurred, using the same eligibility criteria as before.

3.3.5 Fluid Therapy - Hypodermoclysis (HDC)

Patients in Phase II in Edmonton received fluids subcutaneously, using that unit's usual methods⁹⁷. Either 0.9% (normal) saline or a combined solution of 0.3% saline with 3.3% dextrose was usually used. Usually 750 units of hyaluronidase was added to each liter of solution (or 450 units to each half liter bag). Potassium chloride was added to the infusion solution if indicated by the clinical situation or the serum potassium level. The tubing was connected to a butterfly-type needle which was placed into the patient's subcutaneous space, located in the upper arm, chest, abdominal wall, or anterior thigh. The rate of infusion was controlled using an electronic infusion controller. The starting flow rate varied between patients, as did the number of hours per day of infusion. These were reviewed daily, and adjusted if necessary, to obtain optimal fluid balance for each patient, as indicated by clinical assessment, urine output and serum urea and creatinine levels. The site of infusion was checked three times daily and changed when necessary.

3.3.6 Phase II Data Collection Methods

Data on each Phase II patient were collected daily starting on the first day the patient was in Phase II (called day zero). Data were collected on a data recording form, designed prior to starting the study. It was developed with input from staff and pilot tested at the Ottawa unit prior to the study. This form was common to both centres, except the section on monitoring of HDC which was only used at the Edmonton unit. There were multiple data collectors at each centre, including research assistants, nurses and physicians, with involvement depending on several factors such as: data to be collected; workload; availability; and day of the week. Standardization of data collection was optimized by using several methods:

- (1) Assessment scales were agreed upon in advance of the study. Directions for scoring these were included on the data recording form. Tools such as the MMSE were reproduced on separate forms with a new copy used for each assessment of that outcome measure. For these, the final scores were recorded on the data recording form.
 - (2) Investigators from each centre met prior to the study to standardize the assessments for several of the outcome measures.
 - (3) Inservices were held for physicians and nurses at both sites to explain the study and data collection methods.
- Other features of the data collection process were:
- (1) Inter-rater reliability was not measured for any of the outcome measures used.
 - (2) Missing data was minimized as much as possible by having a person available to be a data collector in each centre daily and by having one person in each centre check the data recording forms regularly for completeness.
 - (3) Convenient means were established for the bedside nurses to record measurements of clinical variables they assessed, such as blood pressure, pulse, and fluid intake and output.
 - (4) Any assessment tools requiring direct patient participation were available in both French and English in Ottawa.
 - (5) On the day a patient died, data available for that day were recorded along with the number of hours the patient lived that day.
 - (6) At the end of the study all of the data from both centres were entered onto a computer database in Ottawa.

3.3.7 Outcome Measures Assessed in Phase II

The outcome measures assessed on a planned daily basis are shown in Tables 3.1 and 3.2. They were planned to be assessed in the morning, unless indicated otherwise, starting

on day zero. The outcome measures shown in Table 3.3 were assessed less often than daily, at the planned frequency indicated.

Table 3.1
Phase II Outcome Measures -
Fluid Volume Status Indicators Assessed Daily^{198,199}

Oral mucosa assessment

- 0 - Normal
- 1 - Decreased or thickened secretions
- 2 - Absent secretions

Skin turgor (pre-sternal assessment)

- 0 - Normal - Instant return of skin to rest position
- 1 - Slow return of skin, but within 5 seconds
- 2 - Slow return of skin, taking over 5 seconds

Heart rate

Mean Blood Pressure (bp) (supine and sitting)

= diastolic bp + $1/3 \times$ (systolic bp - diastolic bp)

Table 3.2
Phase II Outcome Measures -
Symptom Measures and Treatments Assessed Daily

Visual analogue scales (100 mm)

- 12 symptoms - pain, activity, nausea, depression, anxiety, drowsiness, appetite, sense of wellbeing, dyspnea, weakness, thirst, and dry mouth
- 0 = symptom absent; 100 = symptom worst
- scored twice daily, morning and evening
- indicated whether patient or staff scored (see text)

Bowel movements - number in previous 24 hours

Vomits - number in previous 24 hours

Pressure ulcers - yes/no
 - location and number at each skin site
 - width and stage of worst ulcer at each skin site
 (see Table B.3 for staging system)

Peripheral edema - yes/no
 - location and proximal extent

Myoclonus

- 0 - No myoclonus
- 1 - Occasional myoclonus less than once in 5 minutes
- 2 - Frequent myoclonus
- 3 - Myoclonus associated with seizures

Level of consciousness

- 0 - Alert (normal)
- 1 - Drowsy, but awake
- 2 - Sleeping, but easy to arouse
- 3 - Stupor - difficult to arouse
- 4 - Coma - unarousable

Delirium Rating Scale (DRS) (see text)

Medications - drugs (including oxygen) actually used by the patient during the previous 24 hours
 - total 24 hour dose of each drug used

Hypodermoclysis - location of needle
 - fluid type and rate of flow
 - duration of flow in the previous 24 hours
 - drugs added to the solution
 - reason for site changes

Table 3.3
Phase II Outcome Measures -
Measures Assessed Less Often than Daily

Fluid Volume Status Indicators:

24 hour fluid intake and output

- done on day 0, unless done as part of Phase II entry assessment
- repeated twice weekly
- results recorded on day measurements completed
- outcomes used were:
 - (1) urine output
 - (2) fluid balance = total intake - total output
 - (3) HDC volume infused (Edmonton only)

Laboratory Investigations

- serum electrolytes, urea, creatinine
- calculated urea-to-creatinine ratio (see text)
- also done - complete blood count, proteins, serum calcium (corrected for albumin level), urinalysis for specific gravity and ketones
- samples taken on day 0, unless performed in the 24 hours prior to Phase II entry
- tests repeated on days #3 and #7 (except for serum albumin and proteins) then every 10 days

Symptom Measures:

Mini-Mental State Examination (MMSE)

- done on day 0, then twice weekly, more often if indicated
- score expressed as a fraction (see text)

Several of the scales were created specifically for this study. These were oral mucosa assessment, skin turgor, myoclonus and level of consciousness. Because of the multiple outcomes requiring assessment each day, the goal was to have quick and simple scales which could be scored by multiple personnel with minimal training. No prior clinimetric validation of these scales was undertaken.

Heart rate and blood pressure were usually measured by the bedside nurse, but the methods used to assess these items

were not standardized between assessors or between units. Patients' weights were not measured because it was felt to be impractical to do for many of the patients, especially those who were bedridden.

Symptoms assessed directly by the patients were done using VASs, with assistance by the nurse if the patient required help. This was an adaptation of the Edmonton Symptom Assessment System (ESAS) which consists of ten VASs for assessing nine specific symptoms and one other symptom of the patient's choosing. For this study, 12 VASs were used, the same nine as in the ESAS plus three others, weakness, thirst and dry mouth²⁰⁰. If the patient was not able to participate in VAS scoring, then a staff member, usually the bedside nurse who knew the patient, scored it. The need for proxy assessment was documented. A single VAS form containing both French and English text was used in Ottawa. Translation from English to French was done at the Ottawa hospital and verified by several staff members, but no back translation occurred.

The MMSE is scored out of 30, with 30 being the best possible score. A score of zero was given if a patient was comatose or was otherwise unable to do any of the items for cognitive reasons. At times a patient was unable to do certain items for physical rather than cognitive reasons. These items were then excluded from that assessment, resulting in a lower maximum obtainable score. Because of this, the scores were proportionally adjusted for missing items by expressing each assessment as a fraction. This produced a score from zero to one, with one being the best score and 0.8 the cutoff between impaired and normal.

A French language version of the MMSE was developed at the hospital in Ottawa with verification of translation by several staff members, but back-translation was not done.

The Delirium Rating Scale (DRS) is a 10 item, 32 point, physician-rated scale for delirium whose rating should be based on at least a 24 hour period, since symptoms of delirium

fluctuate²⁰¹. The best score is zero, with higher scores more likely to be associated with delirium. This scale was validated in a study which included normal subjects and subjects with delirium, dementia and schizophrenia. In the group of 20 subjects with delirium, DRS scores correlated with MMSE scores ($r = -0.43$, $p = 0.033$). Interrater reliability for the DRS was high (interclass correlation coefficient = 0.97). Scores for the delirious subjects ranged from 12 to 30, while the other groups all scored seven or less (normal subjects scored zero or one).

All items for scoring the DRS were assessed daily except cognitive status. When the MMSE was performed, scheduled twice weekly, the result was incorporated into the DRS which was then scored out of 32 on those days. On days when the MMSE was not done, the DRS was scored out of 28. Because of this, each assessment was proportionally adjusted for missing items by expressing the score as a fraction. This yielded a score from zero to one, with zero being the best score.

For the 24 hour fluid output assessment, if a patient was incontinent of urine, the urine volume was estimated in Ottawa by weighing the wet pads and calculating the approximate urine volume contained (knowing the dry pad weights and assuming that one gram of urine was about one millilitre). No estimate of urine volume was made in Edmonton if incontinence occurred.

Because of resource limitations, each centre used its usual laboratory for the analysis of blood and urine samples, and no standardization of their methods was done. Because of this, some laboratory measures had different reference ranges at the two centres, but the results were treated as if they were comparable. The serum urea-to-creatinine ratio was calculated, as a measure of fluid volume status²⁰², using the serum urea in units of mmol/litre and the serum creatinine in μ mol/litre, but was not corrected for the difference in units by multiplying by 1000. The ratio was therefore given as a number less than one. Sodium salts account for more than 90

percent of the osmolality of the extracellular fluids, so changes in measured sodium levels usually represent similar changes in osmolality²⁰³. Because of this relationship, serum osmolality was not measured.

For ease of reporting, opioid doses used were converted to the 24 hour equivalent dose of oral morphine based on the equivalency chart shown in Table B.2²⁰⁴. Patients not on opioids on a particular day were assigned a dose of zero mg for that day and were included in the opioid dose statistics.

The staging system used for pressure ulcers is shown in Table B.3²⁰⁵.

3.3.8 Analysis

Because of the anticipated small sample size, the large number of outcome variables, and the exploratory nature of the study, hypothesis testing using inferential statistics was not done. Descriptive statistics reported include: means, standard deviations, medians, percentiles, maximums, minimums and percentages (for proportions). For the purpose of estimation, 95% confidence intervals (CIs) for the means are given as well.

Most of the data are presented graphically, by site and by time. Because of small sample sizes and some skewed distributions, a non-parametric graphical method, the boxplot, is used for continuous variables in addition to graphs showing means and confidence intervals. The data shown are for a limited number of days or time-blocks because of the sample sizes available. The times shown likely reflect a reasonable time for differences between the groups to have become manifest for most of the variables.

If a particular outcome measure for a patient was not assessed on a particular day, it was treated as missing for that day only. The patient's other available outcome data were still included in that day's descriptive statistics. Sample sizes for the groups are shown in some figures and

tables and represent the number of subjects remaining in Phase II who contributed data for that variable on that particular day.

For Phase II, the a priori analysis plan was to assess each of the outcome variables in a prospective manner, starting from day 0 (called "forward data"). This assumed that the two groups were comparable on day 0, or adjustment for any identified differences could be made. This analysis will be presented first, as the primary analysis.

Phase II Primary Analysis ("Forward Data")

For this analysis, if a patient entered Phase II more than once, only data from the first Phase II time period was used. The analysis of the "forward data" for Phase II compared:

- (1) the fluid volume status indicator outcome measures to assess whether there was a difference between the two study groups with respect to these variables;
- (2) the two groups' symptom-related outcome measures at or very near to day 0 to determine whether their values at the starting point of Phase II were similar enough to allow for comparisons to be made during the rest of Phase II; and
- (3) the two groups' use of treatments other than fluid therapy during Phase II to determine whether they may have confounded any of the symptom measure results.

The measurement of MMSE and 24 hour fluid intake and output were scheduled to be done twice weekly, but were not done on the same Phase II days for all patients. In order to express group descriptive statistics prospectively for these assessments, three-day blocks in time were defined starting at day 0 of Phase II (ie. days 0 - 2, days 3 - 5, days 6 - 8, etc.). If a patient did not have an outcome assessed in a particular three-day block his or her data for that outcome in that block was designated as missing. If a patient had the

outcome measured once in a block, the data from that measurement was used, but if two measurements were made in the same time-block for the same patient the average of the two assessments was used for that patient. Group statistics were then calculated for each three-day block.

Laboratory investigations were scheduled to be done on days zero, three, seven, and seventeen, but some investigations were missed and others were not always done exactly on the scheduled days. For the purpose of expressing group descriptive statistics, each test a patient had done was assigned to the closest scheduled test day. If a test was not done for a particular patient near a scheduled day, that patient's test result was designated as missing for that day.

An operational definition for constipation was used to facilitate the analysis of the bowel movement data. The usual practice of clinicians has been to assess a patient's bowel function at least every three days and to offer to assist the patient in having a bowel movement (BM) if none had occurred during the previous three day period²⁰⁶. Using this guide, it was possible to designate a patient as 'constipated' or 'not constipated' on a particular day: if a BM was documented during the previous three day period, the patient was 'not constipated'; if BM data were complete for the three day period and no BM was documented, the patient was 'constipated' on that day; and if the data were incomplete for the three day period and no BM was recorded, the bowel function status for the patient that day was uncertain and the datum was indicated as missing. Then, starting on day 2 it was possible to determine the proportion of patients who were 'constipated' each day.

Opioid doses were reported as the total 24 hour dose used by the patient. On a patient's last day in Phase II, usually the day of death, only part of the day was available for data collection. The proportion of this day available varied between patients, so opioid doses were considered incomplete

and were treated as missing data on a patient's last day. All other medications were reported as dichotomous variables, indicating only whether or not the drug was used that day, because conversions to common dosage forms were not available for most categories of drugs. For these variables, data for the last day in Phase II were retained.

Phase II Secondary Analysis ("Reverse-Order Data")

If the primary analysis showed that the two Phase II groups differed in some baseline characteristics or outcome measures on day 0 of Phase II, prospective comparisons later in Phase II would be difficult. This is especially true for a descriptive analysis involving a small number of subjects and a large number of variables. To try to adjust for this problem, a secondary analysis of the Phase II data was carried out, in which data from as many patients' as possible were reanalyzed from the perspective of a similar, well-defined point in their illness trajectory, their death. This approach assumed that death would provide a more comparable point for the two populations represented. Although this was not certain, this secondary analysis was carried out, in keeping with the exploratory, hypothesis-generating purpose of the study.

For this analysis, only data from patients who died in Phase II could be used. If a patient entered Phase II more than once, and died in Phase II, only data from the Phase II in which death occurred was used. Each eligible patient's day of death was used to define a common point in time. The days were reversed so that day 0 became the day of death, day 1 became the day immediately before the day of death, and so on. Each day or group of days could then be examined in a manner similar to the forward data.

The length of time survived on the day of death varied. Outcome variables pertaining to medications, fluid intake and output, vomiting, and bowel movements required 24 hours of

data collection and were incomplete for most patients on their day of death, so were removed for this analysis. Other outcome measures were evaluable if they were collected on the day of death, but if not available, they were treated as missing data.

The analysis of the "reverse-order data" compared:

- (1) the fluid volume status indicator outcome measures to assess whether there was a difference between the two study groups with respect to these variables near death;
- (2) the two groups' symptom-related outcome measures for any differences near death; and
- (3) the two groups' use of treatments other than fluid therapy near death to determine whether they may have confounded any of the symptom measure results.

Graphs were prepared with day zero, the day of death, on the left end of the horizontal axis. The days preceding the day of death followed to the right of day zero. Three-day time blocks were used to present group statistics for MMSE, fluid intake and output outcomes and laboratory investigations, with the first time-block being day zero to day two. The laboratory investigations had to be presented in three-day blocks in this analysis because the scheduled days for the tests differed between patients when the "reverse-order" database was created. The definition of constipation was the same as in the primary analysis, except now bowel function status could be determined starting on day zero, the day of death.

3.4 RESULTS

3.4.1 Experimental and Study Populations

Patients were accrued for this study between June 1992 and April 1993. Table 3.4 summarizes the number of patients that made up the experimental and study populations in the two units. In Ottawa, 196 patients were assessed, resulting in 33 evaluable subjects in Phase II. In Edmonton, 92 were assessed

with 33 patients evaluable as well. No patient was excluded in Edmonton because of language, aphasia, or non-cancer diagnosis. In Ottawa, 12 were excluded for these reasons: five did not have cancer, one was aphasic, and six spoke neither English nor French. Another patient, who was on the unit when the study started, was missed during the initial assessments and was not considered for the study. These exclusions are not included in the numbers in the table since demographic information on them was not collected and they did not undergo MMSE testing.

Table 3.4
Experimental and Study Populations
in the Fluid Status Study

	Ottawa (#)	Edmonton (#)
Considered for study	196	92
Excluded	126	39
Consent sought	70	53
Consented for Phase I	52	42
Considered for Phase II	33	37
Entered Phase II	33	35
Evaluable in Phase II	33	33
Died in Phase II	33	27

All of the 126 patients who were subsequently excluded in Ottawa were deemed to be impaired with respect to decision-making capacity according to the assessment criteria for the study. Five of these patients scored 24 or greater on the MMSE, but were excluded because the assessor judged the patient to be incompetent for deciding on participation in the study. Thus, 64% of the patients assessed for the study in Ottawa were excluded because of concerns regarding cognition or competence. Thirty-eight patients in Edmonton were excluded for cognitive reasons (41%). One other patient was excluded erroneously because of the presence of a bleeding disorder and acute renal failure (the protocol called for

admission to Phase I, if the patient consented, then exclusion from Phase II if the patient developed or became at risk of developing a fluid deficit). No patient scoring 24 or greater on the MMSE was excluded in Edmonton.

Out of 70 patients approached for consent in Ottawa, 52 agreed to enter Phase I (74%) and of the 53 approached in Edmonton, 42 agreed (79%).

In Ottawa, 33 out of 52 Phase I patients were considered for, entered and were evaluable in Phase II. One of these 33 patients was initially considered, but HDC was started and the patient was excluded from Phase II at that time. This patient entered Phase II 21 days later and was evaluable. Out of 42 Phase I patients in Edmonton, 37 were considered for Phase II. Two of these 37 were excluded: one because of fluid overload and acute renal failure and another because enteral feedings were being given. Two other patients who entered Phase II in Edmonton were not evaluable: one had no data collected for the first 14 days in Phase II; the other had less than half of the necessary data recorded for the first eight days of Phase II. Both were removed from Phase II when the data deficiencies were discovered.

One patient in Ottawa had two evaluable Phase II periods. The fluid deficit risk resolved the first time and the patient died in Phase II the second time. In Edmonton there were three patients who had two evaluable Phase II periods each. Two of these patients resolved their risks of developing a fluid deficit both times they were in Phase II. Another withdrew consent and left Phase II after two days, but re-entered eleven days later and died in Phase II.

Nineteen patients in Ottawa and five in Edmonton were never considered for Phase II. In Ottawa, ten of these patients died and nine were discharged; in Edmonton, two died, one was discharged and two remained alive in the PCU at the end of the study without being at risk of developing a fluid deficit during the study.

3.4.2 Baseline Unit Admission Demographics

Tables 3.5 and 3.6 present the baseline demographics, assessed at the time of admission to the two PCUs. Data are shown for two groups:

- (1) the total sample of patients considered for the study in each unit (the experimental populations); and
- (2) the subgroup of patients who entered Phase II and were evaluable in each unit (the main study subjects).

For patients who were admitted to the units more than once during the study, the baseline demographics presented were from their first admission.

Differences were noted between the two experimental populations in pain stage, MMSE score, and primary cancer diagnosis. Edmonton's patients had a higher prevalence of stage three pain and a lower prevalence of stage two pain, a higher mean MMSE score, fewer patients with breast and lung cancers and more patients with GI system cancers than Ottawa's patients.

The Phase II sample in Ottawa differed from its parent population in having a higher prevalence of stage one pain, a lower prevalence of stage two pain and a lower prevalence of dysphagia. The proportion of patients with breast and gynecological cancers was higher in Ottawa's Phase II sample than in its total sample while lung cancer was less represented in the subgroup. Edmonton's Phase II sample showed smaller differences in pain staging from its experimental population, but did have a lower prevalence of dysphagia. The prevalence of cancers of the GI system other than from the bowel were less common in Edmonton's Phase II sample compared to the its total sample. The higher MMSE scores in both Phase II samples compared to the respective total unit samples were expected because of the eligibility criteria for the study.

The Phase II samples differed from each other at the time of PCU admission. Edmonton's group had a higher proportion of

males compared to Ottawa, more stage three pain and less stage one pain. The distribution of primary cancer diagnoses differed, with Ottawa's sample consisting of 24% breast cancer patients compared to Edmonton's 6%, while bowel cancer prevalences were 6% in Ottawa and 21% in Edmonton.

Table 3.5
Baseline Palliative Care Unit Admission
Demographics

	Total Samples		Phase II Patients	
	Ottawa n = 196	Edmonton n = 92	Ottawa n = 33	Edmonton n = 33
% male	41	45	36	52
age (years):				
mean	65.9	66.0	64.3	62.8
SD	13.0	11.2	14.3	9.5
median	68.0	67.0	68.0	64.0
min-max	17-96	18-88 (m=1)	31-83	38-74
% with pain stage:				
1	30	24	70	33
2	46	28	6	15
3	24 (m=3)	48	24	52
% with dysphagia	25 (m=7)	24	9	12
6 month Weight Loss (kg):				
mean	10.6	12.1	11.4	12.3
SD	7.0 (m=93)	8.3 (m=20)	6.8 (m=7)	9.2 (m=3)
MMSE score fraction:				
mean	0.51	0.72	0.90	0.92
SD	0.39	0.30	0.06	0.10
median	0.60 (m=16)	0.83	0.90	0.97

m = missing

Table 3.6
Baseline Palliative Care Unit Admission
Primary Cancer Diagnosis

Cancer	Total Sample %		Phase II Patients %	
	Ottawa n=196	Edmonton n=92	Ottawa n=33	Edmonton n=33
breast	16	8	24	6
lung	30	15	15	13
bowel	9	18	6	21
other GI	8	16	9	9
gynecological	6	9	12	12
prostate	8	9	12	9
urinary tract	4	5	3	9
head and neck	4	3	3	0
hematological	6	2	6	0
other	4	8	6	3
unknown	6	7	3	12

3.4.3 Phase II Entry Assessment

The Phase II samples resided for different amounts of time in their respective PCUs prior to entering Phase II, as is shown in Table 3.7. The time-periods shown in this table are from the patients' first admission to their unit until the time of their first evaluable Phase II entry (for most patients their only entry). The mean and median were smaller for the Edmonton sample compared to the Ottawa sample.

Figure B.2 shows the frequency of occurrence of identified causes of patients being at risk of developing a fluid deficit. At Phase II entry, 95% of all patients had a history of poor fluid intake while 13% in Ottawa and 41% in Edmonton had a history of excessive fluid loss. All of the patients who had a history of significant fluid loss also had either a history of poor intake or objective evidence of this on a 24 hour fluid intake and output measurement prior to entering Phase II. The most common causes of patients being

at risk of developing a fluid deficit in Ottawa were anorexia (94%) and decreased consciousness (67%). In Edmonton, the most common causes were nausea (61%) and vomiting (42%). Most patients had more than one cause.

Although our goal was to place Phase I patients into Phase II when they were at risk of developing a fluid deficit, but before it actually occurred, 20 of the Phase II patients in Ottawa and 25 of Edmonton's subjects had a clinical diagnosis of fluid deficiency on entering Phase II. The frequency with which specific symptoms and signs of fluid deficiency were found in this subgroup of Phase II patients is shown in Figure B.3. The most common in both PCUs were dry mouth (by both patient-report and appearance), thirst, decreased skin turgor and decreased urine output. Notable differences between the two centres were the frequency of dry mouth felt by volume-depleted patients (95% in Ottawa, 68% in Edmonton), the frequency of decreased skin turgor found (79% in Ottawa, 42% in Edmonton), the frequency of postural dizziness (58% in Ottawa, 11% in Edmonton) and the frequency of resting tachycardia (65% in Ottawa, 4% in Edmonton). Most patients had several reasons for concluding that they had a fluid deficit: in Ottawa the median number of reasons was six and ranged from four to eight; in Edmonton the median was four with a range of one to five.

The most common route of hydration for the patients at both centres just prior to entering Phase II was oral (31 out of 33 in Ottawa and 28 out of 33 in Edmonton). The intravenous route had been used by one patient in Ottawa and four in Edmonton and one patient in both centres had received hypodermoclysis just prior to being considered for Phase II.

For the patients who were evaluable in Phase II twice (one patient in Ottawa and three in Edmonton), the entry data discussed above pertain to their first entry to Phase II only.

Table 3.7
Time from the First Admission to the Palliative Care Unit
until the First Evaluable Phase II Entry

	Ottawa n = 33	Edmonton n = 33
Mean (days)	31.9	20.2
Standard Deviation (days)	34.6	33.3
Median (days)	23	5
Minimum - Maximum (days)	1 to 175	0 to 132

3.4.4 Phase II Length of Stay and Survival

There were differences between the two Phase II study samples in Ottawa and Edmonton with respect to the time spent in Phase II and with respect to survival, both calculated from the day of entry into Phase II (day 0). Four patients were evaluable in Phase II twice each (one in Ottawa and three in Edmonton); their length of stay data discussed here pertain to their first evaluable entry into Phase II only and their survival is calculated from day 0 of that same entry.

Thirty-two of Ottawa's 33 Phase II patients died during their single Phase II stay. The sole exception remained in Phase II for 25 days, left it for seven days, then re-entered for 14 days, dying during the second Phase II stay. Thus, for Ottawa, length of stay in Phase II is almost the same as survival calculated from day zero of Phase II. Survival time is known for all 33 patients.

Twenty-six of Edmonton's 33 Phase II patients died in their single Phase II stay. The other seven left Phase II; three later re-entered, but only one died in Phase II. Of the six who did not die in Phase II, the date of death of three is unknown. Thus, length of stay and survival differed somewhat in the Edmonton study sample, and survival time is known for only 30 of the 33 patients.

In Table 3.8 the length of stay statistics for the two groups is shown, Edmonton's sample spent a much longer time in

Phase II than Ottawa's. While the median length of stay (26 days) in Edmonton was relatively close to the mean, in Ottawa the distribution was skewed to the right, tending towards shorter stays with a median of only four days. Thus, the amount of Phase II data available from the Edmonton sample was greater than from the Ottawa sample due to the longer stays in Phase II in Edmonton. As a corollary to this, the sample size in Ottawa dropped off more rapidly with time compared to Edmonton (differential censoring), impacting on the comparisons which could be made as time passed in Phase II.

The groups' survival data showed a similar pattern to the length of stay data (Table 3.8). Edmonton's sample survived much longer than Ottawa's after entering Phase II, shown particularly by the difference in the median survivals.

Table B.4 displays the sample sizes remaining in each group for days zero to 14 of Phase II and for selected days after that.

Table 3.8
Length of Stay (LOS) in First Phase II Stay and
Survival from Day 0 of First Evaluable Phase II Entry

	Ottawa (days)		Edmonton (days)	
	LOS n = 33	Survival n = 33	LOS n = 33	Survival n = 30
Mean	11.1	11.7	29.4	37.8
95% Confidence Interval	+/- 5.0	+/- 5.4	+/- 7.9	+/- 11.4
Median	4	4	26	31.5
Minimum - Maximum	0 - 55	0 - 55	1 - 80	1 - 136

3.4.5 Phase II Primary Analysis ("Forward Data")

Fluid Volume Status Indicators

Figures B.4 and B.5 show the changes in the two groups' fluid balances during the first two weeks. By the definition used in this study to identify patients at risk of developing a fluid deficit (fluid intake exceeding measurable output by less than 500 mls), most of Ottawa's group was in negative

fluid balance each time the assessment was done, while Edmonton's group contained a smaller proportion in negative balance. The two groups' means and medians were separated starting with the first three-day time-block (initial measurements were done on many patients after they had entered Phase II and Edmonton's patients would have already started HDC), although the confidence intervals for the means overlapped during the second week of Phase II. Ottawa's values tended to cover a smaller range than Edmonton's. Overall, the two groups showed the expected differences in fluid balances, but also showed a trend to merge with time.

Figures B.6 and B.7 display the urine outputs for the two samples over time. Ottawa's sample had mean urine outputs which wavered at or just above the oliguric volume (400 mls) while Edmonton's means were generally well above this and showed a tendency to rise with time. A difference was already apparent during the first time-block and persisted after that. In each of the three-day blocks following the initial assessment, half or more of Ottawa's subjects, and very few of Edmonton's, were oliguric.

Figures for the clinical assessment of oral mucosal hydration status and skin turgor are not shown. For the former, differences seemed to fluctuate and appeared small most of the time. In both groups, large proportions had mouths which appeared dry, ranging from 20% to 70% during the first week. By two weeks both proportions had reached 100%. Skin turgor in the Ottawa group was worse than in the Edmonton group throughout most of the first two weeks, including the first day of Phase II. Generally, decreased skin turgor was seen in 70% to 100% of Ottawa patients and 20% to 40% of Edmonton patients during the first two weeks.

Heart rate and blood pressure figures are also not shown. Ottawa's subjects had faster heart rates than Edmonton's, even on day zero. On day zero the mean ($\pm$ SD) heart rates were 105.3 ($\pm$ 19.4) beats per minute (bpm) in Ottawa and 92.1 ($\pm$

17.5) bpm in Edmonton. Supine mean blood pressures were fairly equal between the groups. The day zero means ($\pm$ SD) were 77.8 ($\pm$ 18.6) mm Hg in Ottawa and 88.5 ($\pm$ 17.4) mm Hg in Edmonton. Sitting blood pressures were checked too infrequently to be analyzed.

The urea-to-creatinine ratios differed at the first assessment and the difference between the groups remained consistent during the first two weeks of Phase II (see Figures B.8 and B.9). The values were higher for the Ottawa group, consistent with the expected relative fluid deficit compared to Edmonton, yet both groups showed a tendency for the ratio to rise over the two weeks shown. Mean and median serum creatinine levels (not shown) were very close during the first two weeks, except on day three. In the Ottawa group, two patients had high initial serum creatinines which rose considerably, reaching levels of 646 $\mu\text{mol/l}$ and 467 $\mu\text{mol/l}$. This produced a rise in the group mean and a much wider confidence interval on day three. After that, neither of these patients had values available. Otherwise, the two groups' distributions of values for this variable were similar.

Examination of serum sodium levels for the two groups showed little difference (not shown). Both groups had occasional subjects with hypo- or hypernatremia.

In summary, the two Phase II study samples displayed expected differences in some measures of fluid status - skin turgor, heart rate, fluid balance, urine output and the urea-to-creatinine ratio. At each assessment of fluid balance, Edmonton's group had a sizable proportion who, by the study's definition, were in negative fluid balance; however, very few were oliguric. Oral mucosal hydration status, supine blood pressures, serum sodiums and serum creatinines differed little between the groups.

Symptom Measures

Mental Status Measures

The proportions of patients classified into the various levels of consciousness are shown in Figure B.10 for the first two weeks. There were higher proportions of subjects in Ottawa at the poorer levels during the first few days of Phase II.

The MMSE results are displayed in Figures B.11 and B.12 for the first two weeks of Phase II. The two groups already had a large difference in mean MMSE scores at the start of Phase II, with Ottawa scoring worse than Edmonton. The distributions differed - Ottawa's values covered most of the possible attainable scores while Edmonton's were close to or within the normal range, except for a few outliers (as displayed in the boxplots in Figure B.12).

The DRS scores also differed between the two groups starting on day zero, with Ottawa scoring worse. This is shown in Figures B.13 and B.14. The difference decreased during the first week of Phase II. There were more outliers observed in the Edmonton group.

Visual Analogue Scales (VAS)

VAS scores for the two groups are displayed in Tables B.5 and B.6 for days zero, seven and fourteen. There were generally good scores for pain, nausea and dyspnea in both groups. Poor scores were consistently seen for activity in both groups. A difference between the groups appeared to persist for weakness starting on day zero (Ottawa's means were 70 to 80 mm versus Edmonton's 50 mm). The thirst VAS means differed on day zero, with Ottawa worse than Edmonton (close to 50 mm in Ottawa versus about 30 mm in Edmonton); this difference remained on day 14. Dry mouth sensation displayed smaller differences on days zero and seven; however, Ottawa's group was worse on day 14, with mean VAS scores of about 60 mm compared to Edmonton's 40 mm.

Figure B.15 shows the proportions of each group whose VAS scoring was done completely by staff members. There was a 20% difference on day zero, which persisted until day two, with Ottawa requiring more proxy scoring than Edmonton. Generally about one-third to one-half of patients required proxy scoring of the VAS outcomes.

Other Symptom Measures

No figures are shown for this group of variables. Myoclonus was noted more often in Ottawa especially in the first week of Phase II. On day zero, fewer than 10% of either group was affected. During the rest of the first week, zero to 10% were affected daily in Edmonton while 20% to 40% had myoclonus in Ottawa. On some days in Ottawa frequent myoclonus was reported to affect 15% to 25% of patients. No patients had associated seizures in either group.

At the start of Phase II, 48% of the patients in Ottawa and 18% of those in Edmonton had pressure ulcers. The proportion stayed fairly constant in Edmonton during the first two weeks. Ottawa's proportion declined after 10 days to approach Edmonton's before the end of this two week period. On day 14, pressure ulcers were present in 22% of Ottawa's group and 27% of Edmonton's.

The prevalences of edema at the start of Phase II were 58% in Ottawa and 42% in Edmonton, but these converged before the end of the first week.

Vomiting was charted simply as a daily count. Ottawa's group had a slightly higher proportion of patients who did not vomit each day during the first week of Phase II, but both groups had very high daily proportions with no vomiting (70% to 90%) during the first two weeks.

The proportions of each group that were constipated showed a small difference at the start of Phase II (23% in Edmonton versus 29% in Ottawa); this fluctuated throughout the first two weeks. On day six the prevalence of constipation

peaked in Ottawa at 43%, at which time it was 21% in Edmonton.

In summary, the symptom outcome measures used in Phase II demonstrated differences between the two groups from the very start of Phase II, including differences in level of consciousness, MMSE and DRS scores, the need for proxy scoring of VASs, VAS scores for weakness and thirst and the prevalences of pressure ulcers and edema. Myoclonus was more common in Ottawa, but not on day zero.

Treatments

As shown in Figure B.16 for the first two weeks of Phase II, mean daily opioid doses were similar for the two groups. The confidence intervals were wide, especially for Ottawa's group. Median 24-hour oral morphine-equivalent doses differed between the two sites during the first 14 days: in Ottawa it was steady and generally around 100 mg while in Edmonton it fluctuated, from just under 200 mg on day zero to over 700 mg on day 12 (see Figure B.17). Ottawa had outliers using high daily doses of 5000 - 6000 mg, compared to maximum doses of 2000 - 3000 mg used in Edmonton. The distribution of opioid doses in Ottawa consisted mainly of low doses with a few patient outliers receiving very high daily amounts, while in Edmonton outliers were less common, but the group's range (not counting outliers) was much larger. This difference in distribution of opioid doses existed from day 0.

The proportions of each group that used other medications was assessed for ten different categories of drugs, including oxygen. Differences were noted in the use of: sedating agents, anticholinergic agents and antipsychotic agents (Ottawa's proportions greater); and laxatives (Edmonton's proportion greater). See Figure B.18 for sedating agent use and Figure B.19 for laxative use. The use of the hyoscine agents did not differ much between the two groups. There were no real differences in the proportions using antiemetics, coanalgesics, anticonvulsants, corticosteroids, oxygen or

diuretics.

The volume of fluid given by HDC to the patients in Edmonton averaged between 1040 ml and 1302 ml per day when considered in three day blocks over the first two weeks. The median volumes were around 1000 ml per day, but they ranged from as low as 240 ml to 2400 ml per day. The solution used was predominantly the combined solution of 0.3% saline with 3.3% dextrose (used 91% of the time). Normal saline was used 9% of the time.

In summary, there were differences between the groups in the use of several types of medications, other than HDC. Particular differences existed in the use of agents with sedating effects, agents with anticholinergic effects, antipsychotic drugs and laxatives.

3.4.6 Phase II Secondary Analysis ("Reverse-Order Data")

Twenty-seven patients in Edmonton and 33 patients in Ottawa died in Phase II and could contribute to the secondary analysis using the "reverse-order data". The sample sizes in the two centres decreased in a similar way to that seen with the "forward data" Sample sizes are shown in Table B.7.

Fluid Volume Status Indicators

Figures B.20 and B.21 show the fluid balances for the two groups during the two weeks before death. The means and medians as well as the distributions of values for the two groups differed as expected. Ottawa's sample had fluid balances which were almost always below 500 mls per day while 50 to 75% of Edmonton's patients had values which were greater than 500 mls per day. Some of Edmonton's subjects had fluid balances which might have put them at risk of developing a fluid deficit (25 to 50% had a fluid balance of less than 500 mls per day in each three-day block shown).

Figures B.22 and B.23 display the urine outputs for the two groups. The means and distributions differed as expected.

Ottawa's mean and median were close to the value of 400 mls per day while Edmonton's were consistently over 600 mls per day.

The assessments of patients' mouths suggested that dryness was present in over half of the subjects in both groups during the two weeks before death (figures not shown). Near death, Edmonton's group had a prevalence of dry mouth which approached 100% while Ottawa's prevalence was 60% to 80%; however, more severe levels of dryness were more common in Ottawa. Decreased skin turgor was seen more often in Ottawa's group than in Edmonton's (figures not shown). Generally, over 70% had decreased skin turgor in Ottawa, while the prevalence in Edmonton was 40% to 60%. Little change was evident as death approached. Heart rates were generally faster in Ottawa near death. On day zero, the mean heart rates ($\pm$ SD) were 112.0 ($\pm$ 12.3) bpm for Ottawa and 94.6 ($\pm$ 16.4) bpm for Edmonton. Supine mean blood pressures differed little between groups. On day zero the means were 76.3 ($\pm$ 19.4) mm Hg in Ottawa's group and 80.4 ($\pm$ 14.8) mm Hg in Edmonton's. Missing data were prominent with this variable and sitting blood pressure contained too many missing data to be presented. (No figures are shown for heart rates and blood pressures.)

For the laboratory data, there were only a small number of subjects available in each time-block. The serum urea-to-creatinine ratios showed small, inconsistent differences (see Figures B.24 and B.25). The serum creatinine levels were similar, except in the three-day block that included the day of death (figures not shown). Near death, the range of values for this variable in the Ottawa group widened and two outlying values were present; however, the groups' medians remained similar. The serum sodium levels showed no differences between the groups (figures not shown).

In summary, when examining the data from the perspective of the day of death, the two groups differed in fluid balance

and urine output and in the clinical assessment of skin turgor and heart rate, consistent with expectations based on the presumed fluid status of the groups. The assessment of oral hydration status and blood pressure and the biochemical tests seemed to add little to the evaluation of fluid volume status, but the proportion of missing data was significant, especially for the laboratory investigations and blood pressure measurements.

Symptom Measures

Mental Status Measures

Figure B.26 shows the data for level of consciousness. Both groups had higher proportions of subjects with decreased consciousness as death approached, without much difference between the groups. On day zero, close to 50% of subjects in both groups were reported to be comatose or stuporous.

The group means for the MMSE are shown in Figure B.27. One to two weeks before death, the two means were similar and high. Just before death they differed by about 0.2, but had overlapping 95% confidence intervals. As death approached, both groups worsened and just before death the mean MMSE scores were quite low. Boxplots for the MMSE scores are shown in Figure B.28. The distributions of the scores were different for the two groups, especially in the two time-blocks before death. Three to five days before death, 50% of Edmonton's group remained above 0.8 (the cutoff for 'normal') while less than 25% of the Ottawa group was above this level and half were less than 0.1. Just before death both groups had a few patients with normal scores; the remainder of Ottawa's were clustered at less than 0.3 with a median of zero, while Edmonton's were spread between 0.8 and zero with a median of 0.17.

The DRS data are shown in Figures B.29 and B.30 for two weeks before death. Ottawa's means and medians were consistently higher than Edmonton's, without much change in

the difference as death approached, although the 95% confidence intervals overlapped less near day zero. The means and medians tended to increase in both groups as death approached. On each of the four days before day zero, about 25% of the Ottawa group attained scores which were greater than the highest score attained by the subjects in Edmonton on the same day. This occurred on the day of death also, except for one outlying value in Edmonton.

Visual Analogue Scales

The most important aspect of this assessment was the reporting of the VASs. Figure B.31 shows that for both groups the proportion that required reporting by staff instead of by the patient steadily increased from about 40 - 50% about two weeks before death to around 90% at the time of death. No differences between the two groups were seen. Mean VAS scores are shown in Tables B.8 and B.9 for days zero, seven and fourteen. Missing data were prominent, particularly in the Ottawa group on days zero and seven. The proportion missing was worse for certain items such as depression, anxiety and wellbeing in Ottawa and weakness, thirst and dry mouth in Edmonton. The scores obtained did not display clear differences between groups for any of the 12 items. Pain, nausea, depression and anxiety generally were scored low. Activity, drowsiness, appetite, wellbeing and weakness were scored high and tended to worsen as death approached. Dry mouth scores were similar while thirst scores fluctuated and may have been worse in Ottawa, but this was not consistent. Dyspnea scores were a little higher in Edmonton on days zero and fourteen.

Other Symptom Measures

No figures are shown for these variables. Myoclonus was not experienced very often by members of either group, but it was more prevalent in Ottawa and patients with frequent

episodes were more common there during the last two weeks of life. Close to the day of death 10% to 15% of the subjects in Ottawa had myoclonus while fewer than 10% in Edmonton did. Frequent myoclonus was reported in 12% of Ottawa patients on day zero and in none of Edmonton patients.

The prevalences of pressure ulcers were similar prior to the last week of life, then they diverged. The prevalence in Ottawa increased from 46% on day seven to 60% on the day of death, while in Edmonton it decreased from 42% to 22% during the same time period. The prevalences of edema differed two weeks before death (63% in Ottawa versus 42% in Edmonton), but they became more similar in the last week of life. On the day of death the prevalences were 63% in Ottawa and 52% in Edmonton. The frequency of vomiting did not differ between the groups. On most days 80 to 90% of both groups did not vomit. Constipation was generally equal in prevalence, except for some daily fluctuations more than a week before death. The prevalences increased from 13% to 39% in Ottawa and from 12% to 40% in Edmonton from day 14 to the day of death.

In summary, the evaluation of the symptom outcome measures in the reverse-order data suggested that mental status measures worsened in both groups as death approached. The decline in cognitive scores may have occurred a few days earlier in the Ottawa group while delirium scores were consistently worse in Ottawa near death. The groups may have differed in the prevalences of pressure ulcers and myoclonus as well, but differences in the prevalences of edema, vomiting and constipation were not seen. The 12 symptoms assessed by VAS scores did not show any clear differences between the groups, but their interpretation was hindered by the large number of missing data and the frequent need for proxy scoring.

Treatments

Mean daily opioid doses, expressed as the 24-hour oral morphine equivalent doses, were similar for the two groups in the two weeks before death (see Figures B.32 and B.33). The difference on day zero, although appearing large at 300 mg, was rendered insignificant by the large confidence intervals. Median doses differed a small amount, with Edmonton's being larger, and both groups had similar outlying values on each day shown.

Ottawa's group used agents with sedating effects (Figure B.34) and agents with anticholinergic effects more often and Edmonton's group used corticosteroids (Figure B.35) and oxygen more often. Few differences existed in the use of antipsychotics, antiemetics, coanalgesics, laxatives, anticonvulsants or diuretics. Most of the anticholinergic agents were also included in the sedating agent category. When the two hyoscine agents were considered separately, a difference only appeared in the two to three days before death when the use in Ottawa increased. On the day of death, 27% of subjects used these agents in Ottawa while 11% used them in Edmonton.

In summary, there were some differences between groups in the use of four categories of medications which included agents with sedating effects, agents with anticholinergic effects, corticosteroids and oxygen.

3.5 DISCUSSION

3.5.1 Limitations of the Study

This study had several methodological limitations which affected the interpretability of the results. Most important of all, the trial was open and nonrandomized, increasing the risk that various types of biases influenced the results. Although randomization does not guarantee comparable groups, it does allocate treatments without bias. The baseline demographics for the experimental and study populations

demonstrated differences between the groups at the two sites and the proportions of the two experimental populations excluded because of cognitive impairment differed as well. This probably occurred because of the admission criteria and referral patterns for the two PCUs. Several outcome measures assessed at the beginning of Phase II showed that disparities already existed between the study groups. Patients in the two groups may have been at different points in the trajectory of their terminal illnesses at the time of Phase II entry. This possibility was supported by the Phase II length of stay and survival data in conjunction with the clinical data assessed on day zero of Phase II. Selection bias likely contributed to these differences, and may partially explain the difference in the time from PCU admission to Phase II entry for the two study groups. The secondary analysis using the "reverse-order data" placed the groups at a more comparable point on the day of death, but would not compensate for the more intrinsic differences between the groups. It emphasized comparisons in close proximity to death. This was not the initial goal of the study, yet provided the only reasonable means of comparing the small groups with respect to multiple outcomes over time.

The lack of blinding potentially allowed for cointerventions to bias the results (performance bias). The monitoring of pharmacological treatments did show differences in the use of several categories of agents which may have impacted on some of the outcome measures. Non-pharmacological treatments were not monitored, yet may have differed between the groups and affected the results as well. Various physical and psychosocial treatment modalities and spiritual supports are offered in both units. The assessment of many of the outcomes was open to detection bias because of knowledge of the treatment allocation. Validated assessment instruments and explicit measurement scales were used to try to diminish this source of bias.

The Phase II sample sizes were small initially and were

decreased further by the frequent occurrence of missing data and the early losses of subjects, especially in Ottawa. The drop in the number of assessed patients within a few days of the day of death in the "reverse-order data" added to the necessity to emphasize the time period just before death.

The populations accessed were narrow, representing only PCU inpatients with cancer. The sample was narrowed further by the exclusion of all cognitively impaired patients at baseline. Thus, irrespective of the threats to internal validity discussed, the generalizability of the results were limited. The secondary analysis restricted the target population further by focusing on the immediate pre-death period. This time-frame may not necessarily be the most important from the points of view of clinicians, patients and families, although consensus on this is lacking. In the group of six clinical studies that previously examined the effects of fluid status or fluid therapy on the dying, three focused on the period immediately prior to death^{207,208,209} while the other three did not^{210,211,212}. Musgrave enrolled 38 patients with a prognosis of ten days or less, then had to exclude five who lived longer than this time²¹³. Defining the immediate pre-death period prospectively is difficult²¹⁴.

The outcomes monitored were almost all related to physical symptoms and syndromes; except for three VAS outcomes (depression, anxiety and wellbeing) no other measures of psychological, social or spiritual effects were utilized and the impact on the family was not considered. No quality of life measure validated for use with the terminally ill was available at the time of the study.

3.5.2 Implications of the Results

The following discussion refers to the "reverse-order data", unless indicated otherwise.

Fluid Volume Status Indicators

Some of the measures of fluid status were able to reveal the expected differences between the two groups using both the "forward data" and the "reverse-order data". In particular, the fluid intake and output measurements demonstrated the anticipated group differences in daily fluid balance and urine output. Defining adequate fluid balance as a net intake of 500 ml per day assumed that water metabolism by the dying was approximately the same as the general population. This may not necessarily be true; Bruera et al. suggested that the daily amount of fluids needed by dying cancer patients to maintain adequate fluid status was much less than that of the general patient population, averaging only about 1000 ml per day²⁵. In this study, despite hypodermoclysis, a number of patients in Edmonton had fluid balances which were less than the predetermined level used to define a risk of developing a fluid deficit. The courses of individual patients were not analyzed, but regular reassessment of the fluid status of each patient occurred, allowing for the adjustment of infused volumes, if warranted. Urine output was generally well maintained in the Edmonton group compared to Ottawa; the few oliguric patients in Edmonton could have had causes other than volume depletion.

The main biochemical measure of fluid status used in this study was the ratio of serum urea to serum creatinine. The differences here were much more prominent in the primary analysis (with the "forward data") than when assessing the data from the perspective of the day of death. However, the sample sizes for the biochemical measures were smaller in the "reverse-order data" because of the timing of the tests during the study. The similarity in the groups' serum creatinine levels attested to little difference in glomerular filtration rates between the groups²¹⁶. The larger serum urea-to-creatinine ratios seen in Ottawa probably reflected relative extracellular fluid volume depletion rather than other causes.

An increased mean serum urea relative to mean serum creatinine was found in the studies by Waller²¹⁷ and Ellershaw²¹⁸. In both studies, a high proportion of their samples were deemed to be volume depleted, mainly based on biochemical measures.

The finding that the groups in this study had essentially equal serum sodium values was noteworthy because of its similarity to the findings of other studies. Burge's cross-sectional study could detect no relationship between serum sodium and the sensation of thirst and his group's mean and median were within the reference range²¹⁹. Ellershaw's sample had a mean and median within the reference range as well²²⁰. Waller's study found a significantly higher mean serum sodium for the 13 patients receiving IV fluids (148.5 mEq/l) compared to the 55 without an infusion (139 mEq/l)²²¹, although selection bias may have determined this outcome in this cross-sectional study and the overall group's mean was within the reference range. On the other hand, Fainsinger et al. found that in a group of 69 patients receiving HDC, the mean serum sodium (136 mEq per litre) was below the reference range (141 to 148 mEq per litre)²²². Oliver reported that 22 patients who were within 48 hours of death had normal or near normal serum electrolytes, despite no parenteral fluid therapy and despite ten of the patients being uremic. Oliver, however, did not provide the data to support this statement in his brief letter.

The clinical measures of fluid status did not contribute much to the assessment. The distributions of heart rates overlapped a great deal and resting tachycardia has multiple explanations in this population. Assessing postural changes in blood pressure proved to be impractical. The oral hydration status of the two groups looked remarkably similar, with visible dryness being very common in both groups. This probably reflected the multiple causes of dry mouth in this population. Skin turgor was reported to be poorer in a much larger proportion of the Ottawa group, but also was decreased

in about half of the Edmonton group. In an emergency department study of clinical indicators of fluid status in the elderly, three assessments of mouth dryness had moderately strong correlations with volume depletion while skin turgor and tachycardia were only weakly correlated²²³. In a review of the problem of dehydration in older adults, Weinberg et al. stated that signs and symptoms of volume depletion "may be vague, deceptive, or even absent in older persons". Intake and output measurements were seen as unreliable because of incontinence and inaccuracies in charting intake²²⁴. Burge maintained that clinical signs of fluid volume depletion were unreliable in patients with advanced cancer²²⁵.

Summarizing the study's findings regarding measures of fluid status, the use of fluid intake and output measurements plus the determination of serum urea-to-creatinine ratio seemed to be able to differentiate the fluid status of the two groups. Serum sodium did not differ between the groups. Clinical measures lacked accuracy or practicality, except perhaps skin turgor assessment. Drawbacks of intake and output measurements included the possible extra burden it put on patients, family and staff and the frequent errors that occurred because of incontinence or missed measurements. Laboratory data suffered from being missed frequently, from causing increased burden on patients and from being difficult to successfully obtain from many patients. It is probably reasonable to use more than one measure of fluid status in studies on this topic.

Symptom Measures and Treatments

The symptoms experienced by the terminally ill are usually multiple and the causes are multifactorial. Portenoy et al. reported that the mean ($\pm$ SD) number of symptoms present in 243 cancer patients was 11.5 ($\pm$ 6.0), with a minimum of zero and a maximum of 25 symptoms reported by individual patients²²⁶. The issue with respect to fluid

status and fluid therapy is whether they impact to an important degree on the various symptoms and the overall level of distress experienced by the dying, considering the multiple insults to wellbeing that patients face.

There were some differences between the groups in the symptom-related outcome measures. Cognitive status worsened in both groups as death approached, although perhaps it declined a few days earlier in the Ottawa group. The pattern shown by the delirium scores was one of gradual decline in both groups, with Ottawa's group consistently worse. These findings along with the known high incidence of mental status impairment in dying cancer patients and the association of fluid depletion with confusion in the general patient population support performing further studies using mental status as an outcome, as suggested by Bruera et al.²²⁷.

Despite these differences, it was surprising to see little difference in the level of consciousness of the two groups. In contrast, Waller's cross-sectional study within 48 hours of death showed that patients with worse LOC had higher serum sodiums and osmolalities as well as higher urine osmolalities, suggesting a correlation with fluid status (although no correlation was found between LOC and serum urea)²²⁸. The discrepancy between Waller's findings and this study has several possible explanations: the effects of bias in both studies; the different LOC scales used in the two studies; the difference in the study designs; different populations; and different cointerventions.

The VAS scores did not show any clear differences between the groups, but were difficult to interpret since almost all that were completed near death were scored by staff members. Their validity when scored by proxies is unknown, but is questionable. In addition, the proxy scores were intermingled with the patients' own scores²²⁹ and missing data were common.

Myoclonus appeared to have occurred more often in Ottawa

than in Edmonton. Delirium and myoclonus in the terminally ill cancer population have raised the concern that opioid toxicity may be a common cause of both, and potentially prevented by maintaining optimal fluid status and renal function^{230,231}.

Of the other outcomes monitored, only the presence of pressure ulcers of the skin differed between the groups near death, with the group not receiving fluid therapy showing a higher prevalence. An association between pressure ulcers and inadequate fluid intake has been suggested²³². The prevalence of edema was one outcome used to directly assess a potential negative effect of fluid therapy. The prevalences were close to being equal in the few days before death, with Ottawa's, in fact, being a little greater.

Differences in the use of various medications near death could have impacted on the results. Sedating agents and anticholinergic agents can cause or aggravate delirium, but some may also be used to lessen the effects of an agitated delirium²³³. Both were used more often in Ottawa's group; however, antipsychotic drug use did not differ much between the two groups. Steroids have multiple potential effects and side effects which could impact on several outcomes such as cognitive function, edema, nausea, pain, appetite, wellbeing, depression, dyspnea, and weakness²³⁴. They were used more often in Edmonton near death. The reason for the more frequent use of oxygen in Edmonton was not clear. One concern regarding the use of fluid therapy has been that it could cause fluid overload and pulmonary edema; neither were specifically recorded, but the investigators in Edmonton did not notice a problem with this during the study and have reported no problem in their experience²³⁵. There was no increased use of diuretics and hyoscine hydrobromide in Edmonton relative to Ottawa (hyoscine occasionally is used to decrease airway secretions in the dying). This suggested that HDC may not have been associated with more respiratory

problems in Edmonton. Ellershaw's study reported no association between the presence of respiratory tract secretions and fluid status in a group of patients who were within days of death and who were not given parenteral fluid therapy²³⁶.

In summarizing the findings pertaining to symptom-related outcome measures, it must be noted that the most useful comparisons occurred in close proximity to the time of death. Cognitive function, delirium, myoclonus and pressure ulcers deserve further study with respect to their association with fluid status and fluid therapy in the dying. The importance of thirst and dry mouth remain unclear. The role of opioid toxicity should be explored specifically as well, probably in conjunction with the assessment of mental status and myoclonus. What is also needed, and is probably most relevant, is a measure of the impact of fluid status and fluid therapy on the overall wellbeing or quality of life of dying patients. Families need to be included in this assessment of patients' global experience.

Future Research

As discussed in Chapter 2, consensus needs to be reached on identifying the population for whom true uncertainty exists regarding fluid therapy benefits and risks - these are the patients who need to be studied in the future. If an RCT is to be carried out, randomization to intervention groups is ethically acceptable only if there is uncertainty or equipoise with respect to the best treatment to offer²³⁷. Identifying patients for whom fluid therapy is controversial would help define a population in which collective equipoise exists regarding this intervention. A survey of clinicians, patients and families using a series of clinical vignettes in a questionnaire may help to focus a future study on a narrower, relevant population. The series of vignettes should include patients at various stages of their terminal illness, when

preferences and goals of management vary.

Once the relevant population is identified, a double-blind RCT should be considered, comparing fluid therapy by HDC to placebo 'infusion'. The use of placebo raises ethical issues regarding increased burden on the patient and family; there are technical issues as well, but these are probably solvable. This design would leave open the question of the potential effects of the placebo 'infusion' itself - how does the presence and care of an infusion affect the patient and family? Perhaps a third group should be included in such a study, a group with neither a real nor sham infusion. This group would not be double-blinded, but could be randomly allocated and perhaps blinding of the investigator could be maintained.

3.5.3 Obstacles Faced During the Study

While developing the protocol for this study and then implementing and executing it, several obstacles were faced, some of which have been alluded to already. Discussed here are obstacles which were important in this study and particularly relevant to the palliative care setting.

Attitudes and Ethics

Research in the Ottawa PCU was a relatively new endeavour; no study like this had been carried out there before. In contrast, the unit in Edmonton had several years of experience in successfully designing and performing clinical research. As discussed in the previous chapter, there have been concerns within palliative care about submitting patients and their families to research and many workers in the field have protected patients from such pursuits. Although not systematically documented, such feelings existed amongst members of various disciplines on the PCU in Ottawa before the study got underway. Near the end of the data collection phase an informal survey of the staff on

the Ottawa PCU was carried out to determine their attitudes at that point. Twenty-two members responded, 16 nurses and 6 from other undefined disciplines; the denominator was not known. Responses were generally favourable towards research on the unit, with 21 agreeing with the statement that "research is important for the continuation of good patient care." However, four agreed that "we should not bother our patients with research" and four either agreed or were neutral regarding the statement, "In the long run, research will not change the way I care for my patients."

Twelve respondents stated that they had ethical concerns with the research that was done. Comments included: questioning whether the consent form ensured informed consent; emphasizing that patients and families must agree completely with participation before taking part; concerns that excessive laboratory work was counter to the philosophy of the PCU; and stating that some research activities performed hours before death were difficult to accept at times. Four believed that research was a burden on the patient and three felt it was a burden on families, although another five stated that it was only 'sometimes' a burden on families (there were no responses from 11 regarding patient burden and five regarding family burden). Sources of burden mentioned were: bothering a patient who wanted to be left alone; involving a patient whose priorities were on other issues as deterioration occurred; and completing outcome measures which were "difficult and annoying". Some comments regarding the vulnerability of the population were made: concern that patients in a weakened state and newly admitted to the PCU would say yes to a physician as they have in the past (although most consents were obtained by a research nurse); and concern that patients would participate because of fear that their care would otherwise be affected.

These attitudes and ethical concerns need to be considered in any research plans on the PCU as well as in

other palliative care settings. Educating staff about the purposes of clinical research as well as the methods and ethics involved is necessary. Non-research staff could be included on teams planning specific research projects, as well as on committees providing a more global research strategy for a program or service. Throughout a study there should be ongoing monitoring for ethical concerns in addition to methodological and data issues.

Prior to the study there were strong beliefs in both units about the overall benefits or dangers of fluid therapy. The researchers and staff in Edmonton felt that they could not agree to a randomized controlled trial for this study. Ethically they were not able to withhold parenteral fluids from patients who they thought required this therapy. In Ottawa there was an equally strong feeling the other way. Fear pervaded the unit in Ottawa throughout the study because of a perception that the study was trying to prove that parenteral fluids were necessary for the dying. The study became known as the "hydration study" on the Ottawa unit, even though no experimental intervention involving parenteral fluid therapy was used for study patients there. The concept of equipoise and the identification of the patient population for whom equipoise exists with respect to the use of fluid therapy should help make an RCT ethically possible.

Problems with Recruitment

This study assessed a total of 288 patients in both units out of which 57% were excluded because of impaired decision-making capacity, usually due to cognitive deficits. Consent by proxy was not used. The high prevalence of cognitive impairment was much more of a hindrance to recruitment than was the refusal of eligible patients to take part - 76% of all patients approached gave consent. Consent was obtained in advance of most patients' eligibility for Phase II, anticipating that cognitive decline might occur in many

patients. If consent and enrolment had been delayed until patients were at risk of developing a fluid deficit, the number of subjects entered into Phase II would have been even smaller than this study achieved. Twenty of the 31 patients (65%) in Ottawa who had the MMSE measured at the start of Phase II scored low enough to be considered for exclusion from the study if enrolment had occurred at that point. The proportion that would have been affected in Edmonton was smaller, seven out of 33 or 21%. By obtaining consent in advance, when patients were capable of participating in the decision, some exclusions were prevented.

Despite the early enrolment, out of a total of 94 consenting subjects in both centres, 24 were never considered for Phase II: twelve died; ten were discharged before they were eligible; and two were still alive in the Edmonton PCU at the end of the study. Four discharged patients were later readmitted to the Ottawa PCU, but all had declined cognitively in the interim and could not be approached for consent to participate again. Thus, the high prevalence and incidence of cognitive impairment and the unstable condition of patients served as obstacles to recruitment and participation in the study.

Assessment of Outcomes

Missing data were common in both groups, although usually worse in Ottawa. Possible reasons for missing data included: the patient's cognitive, physical or emotional status; concerns of the assessor regarding burdening the patient; and possibly Ottawa's relatively new involvement with clinical research.

Sitting blood pressure was done so infrequently in both groups that it was not analyzed. Only 12 out of 33 patients had it checked on each of the first two days of Phase II ("forward data") in Ottawa, while only four and six out of 33 in Edmonton had it recorded respectively on those days. The

physical limitations of the patients and the staffs' hesitency to burden them by requesting a sitting blood pressure were probably responsible, especially since the supine measurements were done more consistently. However, even those data were missing from 36% of Ottawa's and 18% of Edmonton's patients on day zero of the "forward data". This did not improve during the first week.

Another variable whose assessment was affected by the physical limitations of patients was the MMSE. It was partially completed by some patients because of their inability to use their hands or to see properly. From days zero to 14 in the "forward data", out of 128 MMSEs done in Edmonton, 20 (16%) were scored out of less than the maximum score of 30. In Ottawa the proportion was 18 out of 78 (23%). The proportion fluctuated day by day.

Some variables assessed predominantly by clinical examination of the patient by the doctor were not free from having significant amounts of missing data. The assessment of oral hydration in both groups was not recorded in 10% to 20% of patients on some days during the first two weeks in the "forward data". The "reverse-order data" was better, despite the proximity to death of all the patients. The LOC outcome measure showed a similar pattern of having fewer missing data in the "reverse-order data" compared to the "forward data". DRS scores were missing for one quarter of the patients in Ottawa on days two to four in the "forward data", but were more consistently recorded on other days at the start of Phase II and in Edmonton. Reasons for the high proportion of missing data for these variables was not certain, but may be related to concerns about burdening patients with an assessment for research only.

The pain VAS scores were missing in the Ottawa group in 9% to 50% of cases during the first week of Phase II ("forward data"); in Edmonton this variable had missing data in up to 14% of cases during the same time period. The depression VAS

scores were missing in 31% to 68% of cases during the first week in Ottawa, but much less so in Edmonton (0% to 15%). The VAS scores in both groups were commonly completed by a staff member, and almost all patients near death required a staff member to score them. The need for proxy scoring was probably related to a patient's decreased cognitive function or level of consciousness (if a patient could indicate a score but not mark it, the staff member was to help, but it would have been recorded as patient-scored). The validity of proxy scores is questionable, as is the intermingling of these with the patients' own scores²³⁸. Thus, VAS scores were often missing, and when they were done a fair proportion were scored by a staff member.

Losses to Follow-up

There were a large number of early losses of subjects due to death, mainly in Ottawa. By the fifth day in Phase II, over half of Ottawa's group had died. This would impact on the power of a study, its internal validity and its generalizability. It is particularly relevant to palliative care research since survival is not usually the primary outcome measure, if it is an outcome of interest at all. In contrast to the losses due to death, withdrawals from the study were very uncommon.

3.6 CONCLUSIONS

General clinical recommendations can be made based on the results of this study and there are several conclusions and recommendations from a research perspective as well. For the monitoring of fluid volume status in clinical studies involving the dying, the measurement of fluid intake and output and the use of the serum urea-to-creatinine ratio appear to be useful measures. The intake and output assessments require effort to obtain accurate data. Serum sodium does not appear to reflect differences in fluid status

in the terminally ill population and most clinical signs of volume depletion lack accuracy or practicality, with the possible exception of skin turgor assessment. If clinical monitoring is needed, the use of multiple clinical and, if necessary, laboratory assessments of the individual patient is recommended.

Regarding the clinical management of patients, individualized decision-making is still required with respect to the use of fluid therapy and the benefits and harms of a fluid deficit in dying patients. Consideration needs to be given to multiple factors including: mental status; medications used; other treatments available such as mouth and skin care; and the patient's and family's expectations and preferences.

Much basic science research is needed to examine the physiology of terminal illness with respect to water and electrolyte metabolism. There has been much evidence documented regarding the alterations with aging, including changes in renal function, thirst sensation, renin and aldosterone activities and vasopressin effects²³⁹. Similar research is needed with the dying to identify whether there are specific renal and hormonal changes and what their effects are on fluid needs and fluid balance. Determinants of optimal fluid balance should be defined, then shifts in balance correlated with clinical signs and symptoms as well as overall quality of life.

Some outcomes to consider for use in future studies evaluating the effects of fluid status or fluid therapy on the dying were identified in this study. Mental status measures, including measures of cognitive function and delirium, need to be included along with monitoring for myoclonus and, more specifically, opioid toxicity. Pressure ulcers need further evaluation with respect to the importance of fluid status on this problem in this population. Thirst and dry mouth remain important clinical symptoms which deserve further study,

emphasizing their probable association with each other and their likely multifactorial etiologies. Survival should be included as a secondary outcome. With quality of life measures validated for use in palliative care becoming available soon for use in clinical research, their inclusion in any trial would be mandatory. Finally, the impact of fluid status or fluid therapy on the family needs to be assessed too.

The population which deserves further study with respect to fluid status questions remains unclear. As suggested in the last chapter, surveying clinicians, patients and families may help to define the important population of dying patients for whom uncertainty regarding the best therapeutic choice exists.

Eventually an RCT will be needed to examine the effects of fluid therapy on the dying. Three groups should be considered, one receiving HDC, one receiving a sham HDC and one with no infusion set-up. Blinding should be used as much as possible, at least for the first two groups. A multi-centre trial would be necessary in order to achieve an adequate sample size within a reasonable period of time.

Important palliative care-relevant obstacles faced in this study were: the negative attitudes of staff towards research with the terminally ill; ethical concerns for the subjects regarding vulnerability and burdens; the common occurrence of cognitive impairment affecting eligibility, consent and participation; and the poor and unstable condition of patients, which impacted on recruitment and participation. Outcome assessments were limited by physical as well as cognitive impairments (and likely psychological and spiritual distress as well).

Studying obstacles which are particularly relevant to palliative care clinical research in general continues in the next chapter with a broader and more systematic approach to identifying important issues and their solutions.

CHAPTER 4

OBSTACLES TO PALLIATIVE CARE CLINICAL RESEARCH: A SURVEY OF THREE PALLIATIVE CARE JOURNALS

4.1 SYNOPSIS

Some of the obstacles experienced while designing and implementing the Fluid Status Study were consistent with those apparently faced by the researchers whose work was systematically reviewed in Chapter 2. All of these studies dealt with one clinical problem, but researchers have reported important barriers to palliative care research in general. Up to now they have been reported in nonsystematic reviews of palliative care research, commentaries on the situation, summaries of investigators' own experiences with specific studies and discussions of particular issues.

Obstacles are faced while doing any type of clinical research - palliative care is not unique. Some obstacles are particularly relevant to the palliative care situation because of the nature of the patients, the professional carers involved, the goals of care and the historical background. It is important to identify these barriers in order to optimally plan studies and overall research agendas. It may also be possible to minimize or eliminate some obstacles.

This chapter reports on a systematic approach that was taken to compile a representative collection of obstacles faced by investigators doing palliative care clinical research and to obtain an overview of the type of research that has occurred. A survey of three palliative care-oriented journals was carried out to identify palliative care clinical studies published over a recent two year period. Explicit criteria were used for selecting eligible articles. The papers were read to identify possible obstacles encountered and to label each study with respect to its design and purpose. Only obstacles which were particularly relevant to palliative care were of interest; barriers which posed a hindrance to clinical

research in general were not recorded. This survey identified obstacles faced by researchers who had successfully completed and published a study. It did not explore the issue in studies which never reached publication, but methods of doing so, as a next step, are discussed. A set of obstacles faced by palliative care researchers are presented and some strategies for dealing with them suggested.

4.2 GOALS AND OBJECTIVES

This was a systematic survey of selected journals to identify palliative care-relevant obstacles encountered by researchers while carrying out specific, published palliative care studies. The objectives were:

- (1) to document researchers' experiences regarding relevant obstacles encountered while doing specific palliative care clinical studies;
- (2) to document how researchers dealt with the obstacles faced in these specific, published studies; and
- (3) to identify research designs and purposes in a series of published palliative care clinical studies to obtain an overview of the type of research that occurred and an impression of the effect relevant obstacles had on the choices of designs.

4.3 METHODS

4.3.1 Choice of Journals and Years Surveyed

Journals dedicated to palliative care were considered for this survey. Three journals were selected which have all been peer reviewed since their creation (see Table C.1). They were chosen primarily because they were three of the main palliative care-oriented journals in the world. Other reasons were: they had been published for several years; they came from three different countries; and they were published predominantly in English (the Journal of Palliative Care occasionally publishes in French). The Journal of Pain and

Symptom Management published articles relevant to the overall topic of pain and symptom control, not only in palliative care, but the selection process was aimed at the palliative care studies only.

Relevant palliative care studies were published in other journals as well, for example those whose focus was oncology, general medicine, nursing, psychology, family medicine and pain management. The concentration of articles from these other sources was expected to be much lower and selecting from a vast array of journals would have been more complex. The complexity was heightened by the need to be precise in defining what a palliative care research article was when a wider health care literature population was considered. A survey of a small number of dedicated journals provided a practical and manageable sampling frame for this study.

Prior to the survey, it was known that original research articles made up a minority of the articles published in each issue of these journals. A scan of several issues suggested that between zero and three research articles were published in each issue and that a survey involving two recent years of publications would include about 60 research articles. This number was believed to be practical and probably adequate for gaining a good sense of the obstacles faced.

All three journals published volumes by calendar year and the volumes published during the years 1992 and 1993 were included in the survey. These were the most recent, completed years at the time the survey was initially planned. During this time JPC published eight issues, PM published eight issues and two supplements and JPSM published 16 issues and one supplement. All issues, including supplements, were included in the survey.

4.3.2 Eligibility Criteria for Articles

The selection criteria for articles included were refined during the selection process, but at the end were explicit to

allow for replication of the process.

For the purpose of the survey, a palliative care study was defined as a study in which:

- (1) the study sample very likely included palliative care patients and/or their acquaintances; and
- (2) the results were meant to be generalized to a population which included palliative care patients and/or their acquaintances.

A palliative care patient was defined as a patient whose disease was not responsive to curative treatment and for whom the goal of care was to achieve the best possible quality of life while neither hastening nor postponing death.²⁴⁰ Some studies described their samples in vague terms, such as stating that patients included had "cancer pain" or "advanced cancer". Despite a lack of further qualifications, the assumption was that many of these patients were palliative care patients. Adding to the confidence in including such studies was the fact that the articles came from journals generally oriented to palliative care.

For an article to be selected for inclusion, each of the following criteria were satisfied:

- (1) the article reported on an original, clinically based, palliative care study;
- (2) the study was based on either
 - (a) a pre-determined methodology to answer one or more research questions pertaining to a pre-defined population, utilizing pre-planned, systematic data collection methods or
 - (b) a group of more than ten subjects for which some group results were reported; and
- (3) the article was published in English as a journal article.

Criterion 2(b) allowed for the inclusion of articles which did not clearly describe a pre-determined methodology, but whose size and method of reporting results suggested that

some prior research planning may have occurred. Both prospective and retrospective studies were accepted.

An article was excluded if:

- (1) it reported on a study in which the sample was composed of health care workers only;
- (2) it was a health services study which did not report data from a sample of patients and/or their acquaintances; or
- (3) it was a letter, correspondence or abstract.

Exclusion criterion (3) assumed that these brief reports usually do not contain enough information to determine what obstacles might have been faced during the study.

4.3.3 Identification of Research Design and Purpose

Labels were assigned to each eligible study to identify its main research design and its primary research purpose. The definitions used for the designs were the same as those used in Chapter 2. For this survey, 'Placebo-controlled trials' and 'comparative trials, no placebo' were combined into one design category, 'comparative trials', which were either randomized or non-randomized. Cohort studies were either single group or multiple group cohort studies and either prospective or retrospective.

Table C.2 gives the categories and definitions of primary research purposes used in the survey. This list and the definitions evolved during the selection process (for example, a category called 'survey' was split into 'needs assessment' and 'assessment of knowledge, attitudes and behaviour' while another category called 'audit' was split three-ways into 'satisfaction with care assessment', 'program evaluation' and 'patient profile assessment').

4.3.4 Survey Process

The survey was conducted by one person only and no reproducibility check or blinding was used. No assessment or scoring of methodological quality was included since this was

not the aim of the survey.

All articles in all issues of the three journals over the two year period were considered, applying the eligibility criteria described. During the article-selection process if uncertainty existed regarding the eligibility of an article it was discussed with the thesis supervisor and a decision was reached by consensus. Each article selected was given an identification number for administrative purposes. A list was maintained of articles excluded because they lacked any obvious methodological planning and consisted of a group of only two to ten subjects. This was a quality control measure because of the arbitrary choice of ten subjects as the cut-off point for this eligibility decision, regardless of whether group results were reported or not.

Each selected article was read, labels were assigned for study design and purpose, external funding sources were identified, noting any details provided, and any obstacles definitely or potentially faced by the investigators were recorded, including the rationale for identifying the obstacles. Obstacles noted were only those particularly relevant to palliative care because of its nature, rather than generic obstacles faced by clinical researchers in general. (This did not preclude noted obstacles from being relevant to other areas of clinical research as well.) Details relating to each identified obstacle were recorded, including the means, if any, used to deal with it. Finally, the reviewer surmised whether a better or more appropriate basic research design theoretically could have been used for each study, based on the purpose of the study. Reasons for not using a better design, if stated by the authors, were recorded. (The issue of research design choice was not included to critique the choices of designs, but rather to explore whether important, palliative care-relevant obstacles existed which affected the choices made.) All data were recorded on a pre-designed data form made for this survey, using one form for

each article.

4.3.5 Analysis

The following were enumerated and tabulated: the articles selected; the research designs and purposes; the funding sources reported; and the studies which did not indicate any obstacles. Proportions were expressed where appropriate. Common obstacle themes arising from the eligible articles were identified and used as main headings so that obstacles could be presented in a descriptive, narrative style under these headings. Information derived from the survey was synthesized in this way, referring to pertinent studies. The basic research designs used were compared with theoretically better or more appropriate design choices to determine the proportion of studies which could have used more optimum designs. If the authors of a study gave reasons for their design choice, these were described.

4.4 RESULTS

4.4.1 Articles Selected

Sixty-nine articles were selected, 15 from JPC, 24 from PM, and 30 from JPSM. References for all of the selected articles are listed in Appendix D.

Twenty other articles were excluded because they did not describe an obvious pre-determined methodology and reported on only two to ten subjects. The number of patients reported in these 20 papers ranged from 2 to 10. Two of these reported on ten subjects: one provided case reports with no group statistics²⁴¹, while the other reported on individual cases, but provided a few group statistics as well²⁴². Neither paper provided evidence of pre-planned methodology. No other paper in this set of excluded articles included any group results. Articles which did not present any preplanned methodology and which reported case series (no group results) with more than ten subjects were not enumerated.

4.4.2 Research Designs and Purposes

Table C.3 shows the number of selected articles labelled with each design and purpose. There were no studies which used the following designs: nonrandomized crossover; natural experiment; prospective multiple cohort; or case series. In the design category 'other' there were two studies. One was a therapy study using the experimental, N-of-1 randomized trial design²⁴³. The other used focus groups (nonexperimental) to assess satisfaction with care²⁴⁴.

Twenty of the 69 studies (29%) used group experimental designs and all were therapy studies. Thirteen of these 20 were time series. There were 27 nonexperimental, single cohort studies, making up 39% of the total. The majority of these were retrospective. Cross-sectional surveys comprised 26% of all the studies. Only one study exclusively used a qualitative research design (focus groups), although six others utilized a mixture of quantitative and qualitative methods.

Twenty-five of the studies (36%) were for the primary purpose of evaluating therapies. One was an N-of-1 trial. Seventeen of the 24 therapy studies which investigated groups were uncontrolled (71%). The other 44 studies were fairly evenly distributed amongst the other primary purpose categories. Two designs were utilized for diverse purposes - the single cohort, prospective design was used for seven different purposes and the cross-sectional design was used for nine purposes.

4.4.3 Funding Sources Reported

No source of funding or support was indicated in 46 (67%) of the studies. In the others, acknowledgements were not always clear as to whether support was financial or otherwise, whether financial support was total or partial, or whether funding was specific for the study or provided for the program in general. Also, it was not always clear what type of

organization provided the funding. Interpreting the information provided, the funding pattern appeared to be as shown in Table 4.1. Of the 21 studies whose articles indicated that some form of funding was received, three (14%) were retrospective, while of the 46 for which support was not mentioned, 15 (33%) were retrospective. Seven of the apparently funded studies (33%) were for evaluating therapies.

Table 4.1
Funding Reported by the 69 Studies Included in the
Three-Journal Survey

Support not indicated	46 (67%)
Funding indicated:	21 (30%)
Study specific (total or partial)	14 (20%)
General (for researcher or program)	5 (7%)
Unclear whether specific or not	2 (3%)
Unclear if support financial	2 (3%)
Sources of financial support:*	# of studies
foundations/charities/associations/societies	10
laboratories/pharmaceutical companies	4
funding agencies/government departments	5
type unclear	6
	25
*some studies reported funding from two sources	

4.4.4 Studies With No Obstacles Indicated

In thirty-four of the 69 articles (49%) no palliative care-relevant obstacles could be identified. Some of these contained methodological features (such as a small sample size) which were not explained and which may have had relevant

palliative care obstacles underlying them. The designs and purposes of these 34 studies are shown in Table C.4.

There were 18 retrospective studies in this survey (including the one case-control study). Fourteen (78%) gave no indication of having faced any palliative care-pertinent obstacles. Of the other 51 studies, 20 (39%) did not seem to indicate having faced obstacles. Almost all of these latter 51 studies required direct subject participation, with one exception being a cross-sectional study which accessed medication records only (and did not seem to indicate having faced any obstacles relevant to this survey)²⁴⁵. There was no difference in the identification of palliative care-pertinent obstacles in studies that indicated receiving some type of funding versus those that did not (50% versus 51%).

4.4.5 Obstacles

Four relevant obstacle-themes and several sub-themes arose from this survey. A detailed presentation of the findings is given in Appendix E along with the following: the possible effects of the obstacles; the studies in which these were important along with details from the studies; and strategies used by researchers to deal with the obstacles. The themes identified were:

- (1) patients' conditions - The poor and unstable conditions of patients had several potential effects on a study. These included effects on: recruitment; the informed consent process; the patient's ability to receive the intervention; the patient's ability to be a source of information; the quality of data collected from the patient; the consistency of data collection; and the patient's ability to remain in the study;
- (2) ethical concerns regarding the patient and informal carers - These concerns included: the use of patients and carers as sources of information; the use of investigative technologies; dealing with sensitive issues

- with patients; and concerns about the carer in carer-based studies;
- (3) population heterogeneity; and
 - (4) lack of relevant outcome measures.

4.4.6 Choice of Design

Based on the purpose of each of the studies, it was deemed that a better or more appropriate basic research design could theoretically have been used for 43 of the 69 studies (62%). (For instance, a therapy study using a time series design could have been more appropriately designed as an RCT.) In six of these 43 studies (14%) the authors explained, at least partially, their choice of design. In two, it was simply stated that they were 'pilot studies', and in both the authors called for more research. No further explanations were given and these reasons were not interpreted as being associated with any relevant obstacles. The brief reasons given in four other papers suggested that there were obstacles to using a better or more appropriate design. Although some sounded fairly general, others may have represented issues relevant to palliative care. Walker stated the following in reference to her time series, therapy study, "The three characteristics of true experimental research - control, manipulation and randomization - were not all possible to obtain due to the constraints of the setting and time available."²⁴⁶ The "time available" reason seemed to be a fairly ubiquitous problem in clinical research generally, but the "constraints of the setting" statement may have referred to constraints of the palliative care setting particularly, although she did not specify what these were. Sebastian et al., in their report on a cross-sectional survey for the purpose of providing a patient profile assessment, stated, "...surveys of well planned samples of prevalent cancer cases in the community are the ideal to provide such data. However, such surveys are cumbersome, time-consuming and costly."²⁴⁷

Without any elaboration by the authors, it is difficult to conclude that these reasons are specific for obstacles in palliative care as opposed to research in general, especially considering, as the authors pointed out, that this study was done in India.

In Boyd's retrospective, single cohort, program evaluation study, the retrospective design was used because of concern that the patient and relatives would be distressed by direct involvement in research, especially at a time when they had to cope with a recent admission to an inpatient hospice and the impending death of the patient²⁴⁸. Afterwards they felt better about approaching relatives in a future prospective study, but thought that many of the patients were too ill to answer questions or score symptoms. Burge, although not explaining his choice of a cross-sectional design for his risk factor study, discussed opportunities for future research and said, "Intervention trials for the relief of symptoms may also be conducted now as estimates of the standard deviations of the reported symptoms have been determined."²⁴⁹

4.5 DISCUSSION

4.5.1 Limitations of the Survey

There are some limitations to this survey. All aspects were performed by one person, leaving open to question the reproducibility of the following processes: the selection of articles; the labelling of research design and purpose; the determination of the appropriateness of research design; the extraction of information related to funding, possible obstacles and choice of design; and the categorization of obstacles. Ideally, two independent reviewers should have performed each of the tasks, the level of agreement measured and any disagreements resolved by consensus. Despite this shortcoming, the opportunity to discuss decisions with a second person was available and utilized when a decision on

the eligibility of a difficult article was needed. Disagreements were resolved by consensus. In addition, the process of the entire survey was systematic and was made explicit to allow duplication by others.

In many instances the authors of selected articles probably did not state that relevant obstacles were faced when they existed. The fact that 34 of the 69 articles did not appear to indicate that any obstacles had existed, and, especially that 20 of the 51 non-retrospective studies lacked any such indication, suggested that the information reported pertaining to this sample of studies may have been incomplete. Another indication was that methodological issues clearly existed in several articles and yet they usually were not discussed by the authors. For instance, several of the studies had small sample sizes, but no explanations were provided; relevant obstacles may have been important. Similarly, the fact that very few authors explained their choice of research design, even when a lower quality retrospective design was used, left the impression that a gap in information pertinent to this survey existed.

This survey only looked at articles published in three specifically selected, English language, palliative care-oriented journals during a predetermined two year period. This may not have represented all published palliative care studies. It also did not explore obstacles faced while planning or conducting studies which did not get published or which were published as abstracts, letters or grey literature. Conceivably, a different set of obstacles prevented studies from starting, being completed or getting published as full journal articles.

It was possible that the survey was biased by the exclusion of articles which did not report any preplanned methodology and either included ten or fewer subjects or included more than ten subjects but did not report group results. Perhaps some of these articles dealt with a more

ambitious study which was altered or truncated because of obstacles faced.

Finally, this survey lacked any comparison group of published studies from other clinical areas. The inclusion of such groups would have placed palliative care published research into perspective with respect to other comparable research fields such as geriatrics or with respect to clinical research in general.

4.5.2 Types of Research Published in Palliative Care

Close to two thirds of the studies in this survey theoretically could have used a better or more appropriate design for the designated purpose. One quarter were retrospective in nature. Chart and database reviews have been advocated as part of the first step in doing palliative care research²⁵⁰ and avoid many of the obstacles faced when attempting to carry out research with direct patient participation. There were very few randomized controlled trials, not surprising given the historical development of the area and the belief that randomized trials were particularly difficult to conduct or even unethical in this setting²⁵¹. The fact that 71% of therapy studies assessing groups of patients were uncontrolled attested to an early stage of development of knowledge, a reticence to include control groups or a lack of resources. Even the nonrandomized comparative design occurred only once in the 69 studies.

Very few authors gave reasons for their choice of design. Reasons that influenced the choice may not always have been specifically related to palliative care factors. Some possible, relevant reasons for weaker design choices for therapy studies may have been: the lack of training in research methodologies; the lack of resources to perform a more rigorous study; ethical concerns regarding the involvement of patients directly in research or in more rigorous studies²⁵²; ethical concerns regarding the provision

of an alternate treatment to patients, especially using randomization, as was faced in the Fluid Status Study; and concerns about the difficulty of achieving an adequate sample size in comparative trials in palliative care.

The randomized, crossover design was used slightly more often than the randomized, comparative design, presumably because of the benefits it offered. There are significant tradeoffs though. In contrast to a comparative trial, the crossover design requires a smaller sample size and offers a means of dealing with large inter-patient variability, both relevant advantages in palliative care. On the other hand, it usually requires a longer duration of trial participation by patients and is not robust when dropouts occur. These are important drawbacks in palliative care since patients often are unable to complete even a short study. When using the crossover design the disease is assumed to be stable between the two phases, but this is often not the case in palliative care. By using the patient as his own control, inter-patient variability is removed insofar as the makeup of the comparison groups is concerned, but the design does not prevent population heterogeneity from diluting a true effect present in one or more subgroups or from making interpretation and application of results difficult if large variability of effect is seen.

Qualitative research methodologies appeared to be underrepresented in this sample of studies, although they remain relatively uncommon in health research in general²⁵³. This seems surprising, since these methodologies would appear to be ideal for many of the research questions posed in palliative care, especially with the lack of appropriate outcome measures for this population. This issue has been addressed and the qualitative approach advocated²⁵⁴. Ethical issues have been raised with respect to this specific type of research as well²⁵⁵.

4.5.3 Palliative Care Research Funding

Funding problems were not specifically mentioned as research obstacles in the studies reviewed. Stein et al., in exploring the extent of unfunded research, reviewed original research done in the United States and published in journals of internal medicine and neurology during a one month period in 1991²⁵⁶. Research was considered funded if total or partial support was acknowledged, and investigators were contacted to confirm nonfunding. They found that 45 (23%) of the 196 published studies were unfunded, of which 7% were clinical trials, 9% cohort studies, 18% cross-sectional or case-control studies, 13% surveys, and 53% case series (the working definitions for the designs were not given). Out of 46 studies which gave no indication of funding support in their articles, only one actually had some support. Of the 151 studies that were funded, 79% were funded by U.S. federal sources, 10% by pharmaceutical companies, 10% by nonprofit foundations, and 1% by intramural university research monies. The funded studies consisted of 26% clinical trials, 23% cohort studies, 31% cross-sectional or case-control studies and 20% case series. They surmised that research carried out without specific grant support occurred in the following ways: they were funded by grants received for other projects; some institutions allowed faculty to devote time to research without funding; or investigators were working overtime to do the research.

The results from this palliative care survey showed that 67% of the articles did not acknowledge any funding. If international, palliative care researchers reported their funding similar to the researchers sampled by Stein et al., then the vast majority of these studies were truly not specifically funded. The proportion was much higher than in Stein's sample. The sources of available funds differed as well - in the palliative care survey, out of 19 sources whose type was clear, 52% were foundations, charities, associations,

or societies, 21% were pharmaceutical companies or laboratories, and only 26% were funding agencies or government sources. It appeared that when funding was available it came primarily from sources other than research granting or government agencies, in agreement with the view of the Expert Panel on Palliative Care²⁵⁷ and the reported experience in the United Kingdom²⁵⁸.

Studies using a retrospective design made up 33% of the apparently unfunded palliative care studies, but only 14% of the studies for which some sort of funding was received. Possible reasons why published palliative care research was apparently funded less often than in Stein's study are: the investigators did not seek funding very often or did not know where to look for it; they sought funding from appropriate potential sources, but were turned away more often because of a lack of interest in or understanding of the field²⁵⁹; or they sought funding, but were refused more often because the research proposals presented were inferior to the competition. Were some of the methodologies used because of a lack of funding? For example, were retrospective approaches used because there were limited resources for doing prospective studies, which would have been used if funds were available? Did palliative care researchers go to funding sources with more rigorous designs more often than this sample suggested, but were denied funding and had to downsize the protocols to fit into much smaller budgets? On the other hand, was the apparent lack of funding partially due to the refusal of funding agencies to fund studies of weaker methodologies?

None of these hypotheses or questions take into consideration the research that was not started, completed or published and which may have presented a different pattern of funding status than was seen here. A higher proportion of funded research might be expected amongst a sample of published studies than unpublished or incomplete ones, but the evidence is mixed. One study showed that the publication rate

was significantly higher for studies receiving external funding versus no funding, although there was also a difference between studies externally funded by the drug industry compared to those funded by other external sources (a lower publication rate was found for industry-funded studies)²⁶⁰. Another study found that government sponsorship did not seem to have an effect on publication rate, but pharmaceutical company sponsored studies were less likely to be published than unfunded studies²⁶¹.

The fact that there was no difference in the reporting of palliative care-relevant obstacles in articles that indicated receiving some form of external funding versus those that did not, suggested that reported obstacles faced in published studies were independent of the funding status. This makes sense, since many of the obstacles identified in this survey, such as the poor and unstable condition of patients or the ethical concerns, would not be diminished because of funding, although funding may provide opportunities to lessen the heterogeneity problem.

4.5.4 Obstacles and Possible Solutions

Articles reporting retrospective studies seemed to reveal obstacles much less often than was apparent in the cross-sectional or prospective studies. This would be expected, based on the types of obstacles identified in this survey; they generally involved issues associated with direct subject contact, which retrospective studies avoided. The more general obstacles to performing retrospective studies were not included in this survey.

Recruitment

The poor and unstable conditions of patients was by far the most important obstacle to carrying out palliative care research, affecting participation in several ways. It appeared that recruitment was usually affected more by the

potential subjects' conditions than by eligible patients' refusals to participate. This was noted previously by Bruera²⁶² and observed in the Fluid Status Study. Even the recruitment of lay carers of dying or deceased palliative care patients was affected predominantly by the patients' situation, although perhaps refusals became more prominent in studies of bereaved carers. The effect of various obstacles on recruitment not only impacted on the number of subjects involved in some studies, but also had potential effects on the external validity of the results. Increasing the number of sites for recruitment increased the sample size, but did not solve the generalizability issue. Other solutions considered in some studies were: the involvement of patients at earlier stages of disease; creating and validating proxy outcome measures so many patients would not have to be excluded; and the use of serial measurements of outcomes in anticipation of subject losses rather than excluding high risk patients outright. Other possible methods of dealing with this problem, but not seen in the survey, are: creating and validating non-verbal or behavioural outcome measures²⁶³; obtaining informed consent from the competent patient in advance²⁶⁴, as was done in the Fluid Status Study; and obtaining informed consent by proxy^{265,266}.

Informed Consent

The informed consent process was a crucial issue, considering the high incidence of cognitive impairment, the intense physical symptoms, the use of psychoactive drugs, and the emotional stress present in this population. Some researchers in this survey excluded patients who were unable to provide informed consent, as advocated by others^{267,268}. As noted previously (and as practised in the Fluid Status Study), Bruera recommended formal testing of cognitive function before approaching a patient for entry into a study, excluding those who scored in the impaired range²⁶⁹. Dresser

believed that mental status tests were unsuitable for evaluating decision-making capacity in the research setting. She advocated a task-specific assessment of understanding, appreciation and reasoning²⁷⁰. Examples in the survey suggested that at times investigators may not have been aware that cognitive deficits existed in patients who were approached for consent. When this was the case, the patients may not have been able to provide truly informed consent for research participation.

Other methods of dealing with obstacles to informed consent in this population, but not seen in the studies in this survey, include the following: the involvement of a designated relative or friend, with the approval of the patient, at the time the study is discussed and consent given^{271,272,273}; the provision of information by means in addition to oral and written means, such as by video or audio tapes and computer graphics, to increase the decision-making abilities of mildly impaired subjects²⁷⁴; allowing for both verbal or written consent; obtaining informed consent by proxy when the patient is unable to make decisions^{275,276,277}; and obtaining consent from the competent patient in advance, with the involvement of a designated third party. The latter two methods need to include protective measures - the patient must retain the right to dissent from involvement at any time, irrespective of the level of competence, and assent, when feasible, is necessary for participation. In addition, advance consent ideally should be specific and the designated third party decision-maker should be involved at the time of study entry and during the study as well²⁷⁸. The involvement of patients who cannot give consent on their own should be restricted to studies directly related to the cause of the patients' impaired competence or to needs resulting from their incapacity^{279,280}.

Outcome Assessment

The ability of patients to provide outcome data was limited at times, potentially affecting data accuracy and completeness. In some studies missing data was a major problem, as it was in the National Hospice Study²⁸¹ and the Fluid Status Study. Assessments of patients were limited by: physical frailty; severe symptoms; cognitive impairment; decreased level of consciousness; and ethical concerns. Physical limitations affected a patient's ability to do something as simple as marking a visual analogue scale, as complex as filling out a questionnaire or as involved as participation in an interview. Emotional and spiritual distress presumably also affected a patient's ability to tolerate assessments, to concentrate and to understand the assessments being made. Ethical concerns seemed to involve the investigators' fear of causing patient and caregiver distress or producing increased burden through the assessment of outcomes. McWhinney et al. reported significant problems with caregivers not providing follow-up data, presumably due to their own physical, emotional or spiritual conditions²⁸².

Strategies used or suggested for dealing with obstacles to the assessment of outcomes included: enrolling patients at an earlier point in the disease; training and ongoing supervision of patients and carers regarding outcome assessments; using outcome assessment tools appropriate for the palliative care population - brief, simple and flexible (allowing for verbal or written administration and for choice of preferred tool to use); limiting the number of outcomes assessed at one time; limiting the scope of the study overall; using multiple sources of information, such as a lay carer, staff member or investigator, in addition to the patient; using proxy assessors in place of an incapable patient (although not always valid and data from different sources usually should not be mixed²⁸³); and using serial data. Occasionally it was necessary to measure an outcome using more

than one method in order to assess a method's accuracy. There is a need to create and validate non-verbal, behavioural outcome assessment tools for use in palliative care²⁸⁴.

Losses to Follow-up

The loss of patients early in a study (censored patients) was common, and in some cases the effect was large. This affected the power of the study and potentially both internal and external validity. The most common reason for a loss to follow-up was the death of the patient, but it also occurred because the patient deteriorated and became unable to participate any longer, or because the patient withdrew. Withdrawals appeared to be relatively uncommon in the studies surveyed. A similar pattern of subject losses was seen in the Fluid Status Study, the National Hospice Study²⁸⁵ and McWhinney et al.'s study²⁸⁶. Methods used or suggested to deal with this problem included: excluding patients with a high probability of being unable to complete the study, although this had the potential to slow recruitment and decrease external validity while maintaining internal validity; increasing the sample size goal in anticipation of losses, with the subsequent losses threatening both internal and external validity; recruiting patients from earlier stages of disease only (this would not be appropriate for all research questions); assessing outcomes serially and performing analyses at each time point, including only the surviving subjects at each point (decremental censoring)²⁸⁷; and eliminating all censored subjects completely from the analysis. Other approaches could include: analyzing the data relative to the date of death, as was done in the Fluid Status Study and the National Hospice Study²⁸⁸; and stopping the study if the losses are too large²⁸⁹.

Ethics

Ethical concerns about involving dying patients and their carers in the studies surveyed seemed to focus primarily on the burden such involvement would place on the participants. It was possible that concerns about subject vulnerability also formed part of the undefined ethical dilemma faced. Worry about causing patient and family distress was stated explicitly by several investigators and the use of investigations was raised as an ethical issue in this survey as well as by Ahmedzai²⁹⁰. Other burdens identified previously, but not in this survey, included: the invasion of privacy; the general burden of participation, such as by completing outcome assessments; and the side effects of interventions²⁹¹. Many patients may have taken part in research earlier in their disease as well²⁹².

Methods used to try to lessen the burdens were: limiting the scope of the study, thus decreasing the time and effort required of the patient or the carer; using alternate appropriate information sources, such as the carer or the patient's record instead of the patient directly; and excluding subjects who appeared to be overburdened already. There were several methods used to handle the ethical concerns around sensitive issues, including: using interviews rather than self-completed questionnaires; tape recording interviews to allow the interviewer to listen and respond appropriately; involving a third person of the patient's choosing; avoiding certain sensitive issues; and excluding certain fragile, sensitive or vulnerable subjects. Kristjanson et al. noted additional methods: using brief, simple, multiple choice questionnaires; and hiring data collectors trained in clinical and counselling skills²⁹³.

Carer-based Studies

Recruiting bereaved carers for studies in palliative care was a challenge. Concerns involved issues around

vulnerability as well as burden. There was evidence of the negative emotional impact of being asked to participate, and then of actually participating. Interviews were most commonly used, although one of the studies appeared to use a questionnaire successfully. An interview allowed the interviewer to be available to help the subject, and was seen as being potentially therapeutic. The timing of the interview was crucial and nine months after the death seemed optimal with respect to balancing emotional burden against recall bias. Participation rates were low for some, partially due to the emotional aspects of such studies. Obtaining research ethics board approval was occasionally challenging, as has been reported by others²⁹⁴. Means of dealing with distressed subjects, either at recruitment, during the interview, or after the interview, need to be considered.

Population Heterogeneity

Heterogeneity was noted to be prominent in the palliative care population. Sources of heterogeneity were: age, terminal diagnosis, comorbidity, stage of disease, duration of illness, presence and severity of symptoms, mechanism of symptoms, other treatments received, prognosis, functional status, social situation, and place of care. This list overlapped considerably with Max and Portenoy's list related to pain research²⁹⁵. Most of the studies in this survey dealt with cancer patients primarily, although a few focused on AIDS or ALS patients; however, even in the cancer population there was heterogeneity which may have impacted on the studies.

Heterogeneity may result in dilution of a true effect, nonbalanced groups or a wide variance in the outcome measures. If attempts were made to increase homogeneity by restricting eligibility, recruitment was affected. Other methods used to deal with heterogeneity were: using multicentre trials for access to larger numbers of patients; using the crossover

design to decrease the variability between comparison groups; and using sub-group analyses or multivariate analyses. Kerr suggested stratifying a study sample using important characteristics and developing staging systems to decrease the number of strata needed²⁹⁶. Although he was referring to pain studies, this would apply to other outcomes as well. This was not done in the studies in this survey. In the future, palliative care collaborative research networks may facilitate planning of more multicentre studies. These would permit the assembly of appropriately homogeneous samples of adequate sizes within reasonable time-frames²⁹⁷.

Outcome Measures

Outcome measures for use in palliative care research were either not available or not applicable in some studies in the sample surveyed. Approaches used to deal with this were: the validation of existing measures for use in palliative care; the modification and validation of existing outcome measures; the creation and validation of new outcome measures pertinent to palliative care; and the use of multiple outcome measures where one single measure was inadequate. Qualitative research methods would be useful in the situation where relevant and practical outcome measures are not available, as noted by Davies et al.²⁹⁸, and could be used to help develop and validate measures for use in palliative care²⁹⁹. Quality of life measures are in the process of being developed and tested for use in the palliative care setting^{300,301,302,303}.

4.5.5 Further Exploration of Obstacles

Recognizing the limitations of this survey, there are approaches to filling the gaps in knowledge pertaining to important obstacles to palliative care clinical research. They include the following:

- (1) a survey of other palliative care journals than those included in this survey, especially non-English language

journals;

- (2) a survey of palliative care studies published in non-palliative care publications, using MEDLINE and other computer-based databases to identify articles;
- (3) a survey of palliative care clinicians and researchers to determine their attitudes towards palliative care research and their perceptions and experiences regarding obstacles to doing this research (this would cover non-published studies);
- (4) a survey of other clinical fields, such as geriatrics, to compare their research experiences and obstacles to the palliative care situation;
- (5) a survey of research funding bodies to determine their attitudes and practices with respect to palliative care research;
- (6) a survey of journal editors for their perception of the number and quality of research articles submitted from palliative care; and
- (7) a survey of research ethics boards for their experiences regarding palliative care research.

To assess whether palliative care progresses with respect to clinical research, this survey could be repeated. Two time periods, about five years before and five years after the time of this survey, could be covered by such a duplicate study. Such a study could look for changes in: the types of research done; the funding of studies; the obstacles faced; and the strategies for dealing with obstacles.

4.6 CONCLUSIONS

This survey had limitations, but presented a perspective of the published palliative care research situation and identified a set of obstacles of particular relevance to palliative care clinical research. Most of the research identified was made up of descriptive studies and uncontrolled

trials. Important factors which may have impacted on the types of clinical research done in palliative care as seen in this survey were: the early stage of development of palliative care research; negative attitudes of staff towards research with the dying; ethical concerns regarding burdening of patients and carers, their vulnerability and the use of randomization and control groups; the unstable condition of many patients; and the lack of specific research funding.

Obstacles which were particularly relevant to palliative care clinical research and which were identified in the background information in Chapter 2, the Fluid Status Study in Chapter 3 and this survey are amalgamated into the following list of obstacles:

- (1) Negative attitudes of palliative care staff towards research with the dying;
- (2) Ethical concerns regarding: the vulnerable population; burdening of patients and carers; and methodological issues including randomization and the use of comparison groups. The burden on research subjects occurs from measuring outcomes, invading privacy, performing investigations, performing interventions and causing side effects;
- (3) Lack of trained palliative care researchers and access to research expertise;
- (4) Lack of an appropriate proportion of the available research funding for palliative care clinical research;
- (5) The poor and unstable condition of palliative care patients affecting: recruitment and eligibility; the informed consent process; the patient's ability to receive an intervention; the patient's ability to provide accurate and complete information; and the patient's ability to remain in the study for a sufficient duration;
- (6) Lack of clear agreement on the definition of the palliative care population;
- (7) Heterogeneity of the palliative care population with

respect to multiple factors;

- (8) Limited access to large numbers of palliative care patients to approach for enrolment into clinical studies;
- (9) Lack of relevant, practical and validated outcome measures for use in palliative care.

Some of these obstacles cannot be diminished or eliminated; they are inherent in the population. Researchers need to acknowledge and accommodate them when planning studies or research agendas. Others are theoretically responsive to maneuvers to decrease their importance or even to eliminate them. These are: negative attitudes; lack of training; lack of funding; lack of a clear definition for the palliative care population; limited access to potential subjects; and lack of relevant outcome measures. Population heterogeneity may decrease if the population definition narrows the target audience, but this is unlikely. The clinical coverage by palliative care will probably widen^{304, 305, 306}.

Many strategies for dealing with obstacles were identified and summarized in the discussion of this survey. Some strategies of global relevance to palliative care research are summarized here.

- (1) Education of palliative care staff and researchers should be used to diminish the negative attitudes towards clinical research, and to clarify ethical concerns regarding issues such as randomization and the use of control groups (in particular, the concept of equipoise). Staff could be included in research planning.
- (2) Due to the lack of a clearly defined palliative care population, each study must clearly and specifically define the experimental and target populations which are relevant to the research question. The development of classification or staging systems would help here.
- (3) The potential burden of research on patients and their caregivers needs to be recognized and minimized by the investigators.

- (4) The vulnerability of the palliative care population, including the patients and their families, is real and significant. This must be recognized at all stages of planning and execution of a study, and the research role of the investigators must be made clear to potential subjects. Ideally, a non-clinician should approach the potential subjects regarding participation in a study. Ethical monitoring of a study could be included in the protocol.
- (5) Community participation, consisting of patients, families and support groups/consumer groups, could contribute to the planning of a research agenda of a program as well as the development of specific studies. They could provide several possible benefits:
 - (a) They can help in the selection of relevant research questions to test and important outcomes to assess;
 - (b) They can advise on ethical issues, such as informed consent, amount of potential burden on subjects and design choices;
 - (c) They can provide advice on means of optimizing recruitment;
 - (d) Their involvement may help to change the attitudes of staff who are resistant to palliative care research; and
 - (e) Their involvement may result in a lobby for increased resources for palliative care research^{307, 308}.
- (6) The creation of a collaborative palliative care research network for the purpose of designing and executing multicentre studies in palliative care would have several distinct advantages:
 - (a) It would provide access to larger numbers of palliative care patients, allowing for larger sample sizes, faster recruitment, increased generalizability and diminished importance of the

heterogeneity problem;

- (b) It would permit more studies to be done because of the larger pool of patients available;
- (c) It would allow for a larger source of hypotheses and research questions to generate into protocols;
- (d) It would allow for easy sharing of research expertise and resources; and
- (e) It may result in the production of stronger research protocols with a better chance of obtaining external funding.

Such a group was recommended in Canada by the Expert Panel on Palliative Care in 1991³⁰⁹ and the Canadian Palliative Care Clinical Trials Group was created shortly afterwards, initially funded by a pharmaceutical company. Palliative care programs at the University of Alberta, McGill University and the University of Ottawa were the initial members. Collaboration between academic centres and non-academic centres would be beneficial as well. The non-academic programs lack research expertise, usually want to be involved with research and have access to patients³¹⁰. Linkages with other clinical programs, such as cancer centres, would further increase access to patients, research expertise and resources³¹¹ while increasing the research experience of the palliative care investigators.

- (7) Pilot studies could be used more often prior to a major multicentre study, in order to determine the feasibility of doing the larger study and to help in its design. Information could be obtained on access to patients, recruitment, compliance with the intervention, the use of outcome measures, the rate of subject losses and the amount of burden on subjects³¹².

CHAPTER 5

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.1 SUMMARY

In the process of studying how fluid status and fluid therapy impact on the dying, the challenges of planning and conducting clinical research in palliative care were prominent. The clinical problem represents a typical palliative care research topic, one which is controversial and which has wide relevance to all settings where care is delivered to the terminally ill. However, it was not investigated without facing important and common impediments. These obstacles are not unique to this setting, but are particularly relevant because of the nature of palliative care. They need to be recognized and considered in order for effective research to occur.

A systematic review of the published health care literature was carried out to determine the state of knowledge that existed concerning the effects of fluid status and fluid therapy on the dying. A small number of recently published, descriptive studies were identified which provided questions for further research as well as methodological and ethical issues for consideration. A nonrandomized comparative trial of fluid therapy for dying patients in two palliative care units was then reported (the Fluid Status Study). Multiple outcome measures were assessed in this hypothesis generating study and the possible effects of fluid therapy on various symptoms and fluid status measures were examined.

Obstacles to doing palliative care clinical research were reviewed, supplemented by the studies identified in the systematic review and the experience of conducting the Fluid Status Study. A systematic journal survey was performed to identify obstacles of particular importance to palliative care clinical research in general and to suggest some means of dealing with them.

5.2 CONCLUSIONS

5.2.1 Fluid Status and Fluid Therapy

With respect to clinical care, individualized decision-making remains necessary. This should include consideration of the patient's symptoms, mental status and medications as well as the patient's and family's expectations and preferences. In clinical research settings, the measurement of fluid intake and output and the determination of the serum urea-to-creatinine ratio are useful measures of fluid status for groups of patients while serum sodium is not. Most clinical measures of fluid status lack accuracy or practicality.

Thirst and dry mouth are common in the dying, have multiple causes and are closely related to each other. The role of fluid status and fluid therapy in affecting their severity and the distress they cause and in providing relief is unclear.

Cognitive impairment (including delirium), myoclonus, pressure ulcers and opioid toxicity deserve further study of their possible association with fluid status.

5.2.2 Obstacles to Palliative Care Clinical Research

Much of the research done in palliative care is made up of descriptive studies and uncontrolled trials. Nine important obstacles of particular relevance to palliative care clinical research are:

- (1) negative attitudes of staff;
- (2) ethical concerns;
- (3) lack of trained researchers and research expertise;
- (4) lack of adequate funding;
- (5) the poor and unstable condition of patients;
- (6) lack of a clear definition of the palliative care population;
- (7) heterogeneity of the palliative care population;
- (8) limited access to patients;

- (9) lack of relevant, practical and validated outcome measures.

5.3 RECOMMENDATIONS

5.3.1 Fluid Status and Fluid Therapy

- (1) Clinical management regarding fluid status must continue to be individualized for each patient and should include consideration of mental status, medications being used, expectations and preferences.
- (2) The measurement of fluid intake and output and determination of the serum urea-to-creatinine ratio can be used to assess the fluid status of groups of patients in clinical studies.
- (3) Basic science research is needed to study the physiology of water and electrolyte metabolism in the dying.
- (4) Outcomes to include in further research on the effects of fluid status and fluid therapy include: mental status; myoclonus; opioid toxicity; pressure ulcers; thirst and dry mouth; quality of life; and family impact. Survival should be a secondary outcome.
- (5) Consensus methods are needed to identify the population of terminally ill persons who need to be included in future studies.
- (6) A double-blind RCT is needed to evaluate the effects of fluid therapy on dying patients.

5.3.2 Obstacles to Palliative Care Clinical Research

- (1) Obstacles should be investigated further by surveys of other literature sources and relevant institutions or personnel.
- (2) The progress of research should be assessed by repeating this survey to cover different time periods.
- (3) Education of palliative care staff and researchers is needed regarding attitudinal and ethical issues.
- (4) Palliative care staff should be involved in research planning.
- (5) Ethical monitoring of studies should occur.

- (6) Community participation in research planning should occur.
- (7) Collaborative palliative care research networks should be created.
- (8) Pilot studies should be used more often.

In closing, the following quotation by Dunphy et al. is fitting. It was taken from an article dealing with the controversy surrounding fluid therapy for the terminally ill.

The ethics of conducting such research might well be problematic, but we might also question the ethics of continuing to manage patients in a particular fashion without the scientific evidence to support this approach.³¹³

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APPENDIX A

SYSTEMATIC REVIEW TABLES

Table A.1
Palliative Care Journals Searched by Hand
for the Systematic Review

Journal	1st Year of Publication	Most Recent Issue Searched
Hospice Journal	1985	10 (4)
Journal of Palliative Care	1985	12 (1)
Journal of Pain and Symptom Management	1986	11 (5)
Palliative Medicine	1987	10 (2)
Progress in Palliative Care	1993	4 (1)
European Journal of Palliative Care	1994	3 (1)

Table A.2
Books Searched for the Systematic Review

(1)	Doyle D, editor. Palliative Care: The Management of Far-Advanced Illness. Beckenham: Croom Helm, 1984.
(2)	Twycross RG, Lack SA. Control of Alimentary Symptoms in Far Advanced Cancer. Edinburgh: Churchill Livingstone, 1986.
(3)	Zimmerman JM. Hospice - Complete Care for the Terminally Ill. Baltimore: Urban & Schwarzenberg, 1986.
(4)	Mosley JG. Palliation in Malignant Disease. Edinburgh: Churchill Livingstone, 1988.
(5)	Lynn J, editor. By No Extraordinary Means - The Choice to Forgo Life-Sustaining Food and Water. Bloomington: Indiana University Press, 1989.
(6)	Twycross RG, Lack SA. Therapeutics in Terminal Cancer. 2nd ed. Edinburgh: Churchill Livingstone, 1990.
(7)	Saunders C, Sykes N, editors. The Management of Terminal Malignant Disease. 3rd ed. London: Edward Arnold, 1993.
(8)	Patt RB. Cancer Pain. Philadelphia: J. B. Lippincott, 1993.
(9)	Doyle D, Hanks GWC, MacDonald N, editors. Oxford Textbook of Palliative Medicine. New York: Oxford University Press, 1993.
(10)	Doyle D. Domiciliary Palliative Care - A Guide for the Primary Care Team. New York: Oxford University Press, 1994.
(11)	Twycross R. Pain Relief in Advanced Cancer. Edinburgh: Churchill Livingstone, 1994.

Table A.3
Methodologic Quality Instrument

1. Study design (choose 1 only):

- | | |
|--|---|
| <p>Experimental, randomized*:</p> <p>☐ Placebo-controlled trial</p> <p>☐ Comparative trial, no placebo</p> <p>☐ Crossover trial</p> <p>Experimental, nonrandomized**:</p> <p>☐ Placebo-controlled trial</p> <p>☐ Comparative trial, no placebo</p> <p>☐ Time series trial</p> <p>☐ Crossover trial</p> <p>☐ Natural experiment</p> | <p>Nonexperimental:</p> <p>☐ Cohort, prospective</p> <p>☐ Cohort, retrospective</p> <p>☐ Cross-sectional</p> <p>☐ Case-control</p> <p>☐ Case reports or case series</p> <p>☐ None of the above (describe below)</p> |
|--|---|

2. What was the study question? (please use the space below)

- [responses to items 3-24: ☐ Yes ☐ Partial ☐ No ☐ Not applicable]
3. ☐ Was the study question sufficiently described?
 4. ☐ Was the study design appropriate to answer the study question?
 5. ☐ Were both inclusion and exclusion criteria specified? (If case study, check N/A.)
 6. ☐ For case studies only: Were patient characteristics adequately reported? (If not case study, check N/A.)
 7. ☐ Were subjects appropriate to the study question?
 8. ☐ Were control subjects appropriate? (If no controls were used, check No.)
 9. ☐ Were subjects randomly selected from the target population?
 10. ☐ If subjects were randomly selected, was the method of random selection sufficiently well described? (If subjects were not randomly selected, check N/A.)
 11. ☐ If subjects were randomly allocated to treatment groups, was the method of random allocation sufficiently described? (If subjects were not randomly allocated, check N/A.)
 12. ☐ If blinding of investigators to intervention was possible, was it reported? (If not possible, check N/A.)
 13. ☐ If blinding of subjects to intervention was possible, was it reported? (If not possible, check N/A.)
 14. ☐ Was measurement bias accounted for by methods other than blinding?
 15. ☐ Were known confounders accounted for by study design? (If no confounders, check N/A.)
 16. ☐ Were known confounders accounted for by analysis? (If no confounders, check N/A.)
 17. ☐ Was there a sample size justification before the study?
 18. ☐ Were post hoc power calculations or confidence intervals reported for statistically nonsignificant results?
 19. ☐ Were statistical analyses appropriate?
 20. ☐ Were the statistical tests stated?
 21. ☐ Were exact p values or confidence intervals reported for each test?
 22. ☐ Were attrition of subjects and reason for attrition recorded?
 23. ☐ For those subjects who completed the study, were results completely reported?
 24. ☐ Do the findings support the conclusions?

* original instrument included 'Time series trial' in this group - item removed for this review

**original instrument used term 'unrandomized' - term changed for this review

Table A.4
Definitions Used for Study Designs

Experimental	an intervention is employed
Comparative Trial	parallel groups compared
Time Series	single group with each subject as own control
Crossover	two groups of subjects start different treatments, then switch
Natural Experiment	intervention applied by someone other than the investigator
Cohort	one or more groups followed over time, selected by risk factors
- Prospective	sample defined and risk factors assessed before outcomes occur
- Retrospective	sample defined and risk factors assessed after outcomes occurred
Cross-sectional	all measurements made at one time for each subject
Case-control	groups selected by outcomes
Case report/series	no control subjects and results reported for individual(s), not for group (personal communication, M. K. Cho)

Table A.5
Scoring System for Methodologic Quality Instrument

Item	Points
Design:	
Experimental, Randomized:	
Placebo-controlled	10
Comparative	9
Crossover	9
Experimental, nonrandomized	
Placebo-controlled	7
Comparative	6
Time series	5
Crossover	6
Natural experiment	2
Nonexperimental	
Cohort, prospective	4
Cohort, retrospective	3
Cross-sectional	2
Case-control	2
Case reports/series	1
Questions 3 - 24 responses:	
Yes	2
Partial	1
No	0
Not applicable	0
Final score:	
Total Points divided by total possible points (excluding "Not applicable" items) gives a final score between 0 and 1, with 1 representing the highest quality.	

Table A.6
Description of Column Headings in Table for Data Synthesis

Study	identified by last name of first author and by year of publication
Design	methodological design; was blinding used?
Purpose	purpose stated in the article
Participants	total sample size; description of subjects - key eligibility criteria (age; sex; diagnosis; stage of disease); how accessed; how selected; comorbidity; prognosis at entry; survival
Exclusions	number of potential subjects excluded and reasons; characteristics compared to included subjects
Groups	number in each group; description of comparison groups;
Interventions	types; amounts; duration; goals
Fluid Status Assessments	how assessed and by whom; how defined
Covariates	possible confounders measured, by whom and how
Outcomes	outcomes assessed; specific tools used; who performed assessments and how
Follow-up	frequency and duration
Analysis	narr = narrative only; desc = quantitative-descriptive; inf = quantitative-inferential.
Quality Score	final score (0 to 1) based on assessment with the methodologic quality instrument
Results	as reported in article for each outcome measure
Conclusions	authors' conclusions or recommendations
Comments	reviewer's comments regarding important flaws (gaps; possible biases; missing data; do results support conclusions made?)

Table A.7
Design Characteristics of Studies Included in the Systematic Review of Published Clinical Research on
the Effects of Fluid Status or Fluid Therapy on the Dying

Study	Design	Purpose	Participants	Exclusions	Groups	Interventions
Burge 1993	cross-sectional; no blinding	What is the severity and distribution of symptoms possibly associated with dehydration in inpatient palliative care patients? What is the association between these symptoms and objective measures of dehydration?	- n = 52 - selected from PCU admissions with: - age $\geq$ 18 - advanced cancer - prognosis $\leq$ 6 weeks - speak English or French - able to understand, consent to, and take part in study (assessed by nurse and researcher) - mean age 64.4 - M/F = 26/26 - 27% died within 2 weeks of study	- n = 71 - confusion(20) - weak(17) - drowsy/coma(13) - language(7) - died(5) - refused(5) - aphasia(2) - anxiety/agitation(2) (survival shorter, fluid intake less, needed more mouth care assistance than participant group)	not applicable	- PCU care for all - parenteral fluids allowed and received by a few patients (personal communication with author); no details given

Table A.7 (Continued)

Study	Design	Purpose	Participants	Exclusions	Groups	Interventions
McCann 1994	prospective single cohort; no blinding	Does limiting food and fluids to only that requested by terminally ill patients have adverse effects on quality of life?	- n = 32 - selected from a comfort care unit in long-term care facility - terminally ill - cancer(31); stroke(1) - prognosis $\leq$ 3 months - mean age 74.7 - M/F = 9/23 - mentally aware at admission and for $\geq$ 75% of time before death - mean length of stay 40 days (4-199) - all died in unit	- n = 16 - expressed needs inconsistently - in "various stages of coma or delirium" - no specifics given about the group	not applicable	- inpatient team care for all - no parenteral fluids

Table A.7 (Continued)

Study	Design	Purpose	Participants	Exclusions	Groups	Interventions
Waller 1994	cross-sectional; no blinding	Are cancer patients dehydrated close to death? Do IV fluids affect the hydration status or level of consciousness of cancer patients close to death?	- n = 68 - hospice cancer inpatients - no demographics given - lab tests done within 48 hours of death (selections occurred after death)	- presumably any patient who did not die in the hospice or lab work within 48 hours of death - number not given - not described	- 55 no IV - 13 with IV	- inpatient hospice care for all - IV fluids for some; generally 1-2 l./day "to maintain reasonable fluid intake"; types/duration not given
Ellershaw 1995	prospective single cohort; no blinding	What relationship do respiratory tract secretions, thirst and dry mouth have with level of hydration, as measured by biochemical parameters, in the terminally ill?	- n = 82 - hospice inpatients - advanced cancer - median age 73 - M/F not given - with daily review, a patient entered study when seen to be dying plus taking sips only or unable to take oral meds - all died within 5 days of study entry	- if nurse or doctor thought involvement not appropriate - number not given - not described	- at initial assessment: - 61 biochemically dehydrated - 21 not biochemically dehydrated	- PCU care for all - no parenteral fluids

Table A.7 (Continued)

Study	Design	Purpose	Participants	Exclusions	Groups	Interventions
Bruera 1995	retrospective natural experiment; no blinding	What was the occurrence of impaired mental status in PCU patients before and after implementing 3 measures: regular cognitive testing (MMSE), aggressive hydration, opioid rotation?	- n = 279 - all PCU inpatients during two past time periods - advanced cancer - mean age 65-66 - M/F = 126/153 - 97% died in PCU with average stay of 33-41 days	- using haloperidol for nausea - number not given - not described	- 117 in 1st. time period (1988-1989) - 162 in 2nd. time period (1991-1992)	- PCU care for all 2nd. time period new measures used: - regular MMSE - hypodermoclysis and opioid rotation used with early cognitive changes - hypodermoclysis - mean volume of 1083-1159 ml/day; fluid types, durations, and goals not given
Musgrave 1995	cross-sectional; no blinding	What are the effects of intravenous fluids on dying patients?	- n = 19 - inpatient adult oncology unit - terminally ill with prognosis $\leq$ 10 days - receiving IV fluids - group demographics not given	- n = 19 - survival > 10 days (5) - died without IV (1) - transferred (2) - semi/unconscious (11)	not applicable	- hospital care for all - IV fluids received by all - fluid types, durations and goals not given - volumes 500 - 3000 ml/day

Table A.8
Characteristics of Studies Included in the Systematic Review of Published Clinical Research on
the Effects of Fluid Status or Fluid Therapy on the Dying
- Assessments, Method of Analysis and Methodologic Quality Score

Study	Fluid Status Assessments	Covariates	Outcomes	Follow up	Analysis	Quality Score
Burge 1993	- 24 hour fluid intake estimate by nurse - serum sodium, urea, osmolality	from chart: - age - drugs - oral disease - survival by nurse: - mouth care	by patients: - 100 mm VAS for thirst (average experience over previous 24 hours) - VAS for dry mouth, taste, nausea, pleasure in drinking, fatigue, pain (all 6 not used in analysis)	none	inf	0.58
McCann 1994	none	none	by patients: - hunger (dichotomous) - thirst/dry mouth (dichotomous) by patient and family: - discomfort numerical analogue scale (0 to 10); if patient unable, then judged by family and team - amounts & types of food/fluids used and their effects - after death, team categorized overall comfort by consensus	- several times per day - admission to death	desc	0.36

Table A.8 (Continued)

Study	Fluid Status Assessments	Covariates	Outcomes	Follow up	Analysis	Quality Score
Waller 1994	- serum urea, creatinine, sodium, osmolality - urine osmolality - compared to "normal values"	none	- alertness scale (1 to 4) - not stated who assessed this	none	inf	0.36
Ellershaw 1995	- not biochemically dehydrated if: - serum osmolality 274-295 mOsm/kg - serum sodium 133-148 mmol/l - serum creatinine <130 umol/l - serum urea <12mmol/l - otherwise biochemically dehydrated	not stated who assessed: - respiratory infection (sputum colour or use of antibiotics) presumably from chart: - lung cancer primary - use of drugs causing dry mouth	not stated who assessed: - respiratory tract secretions (audible or use of hyoscine hydrobromide in previous 12 hours) by patient: - dry mouth (dichotomous) - thirst (dichotomous) after death data collection (not stated by whom; presumably from chart): - presence of respiratory secretions since initial assessment - persistence of respiratory secretions despite hyoscine use	initial assessment only, then data collection after death	inf	0.41

Table A.8 (Continued)

Study	Fluid Status Assessments	Covariates	Outcomes	Follow up	Analysis	Quality Score
Bruera 1995	- daily examinations - weekly blood work (neither data given)	from chart: - age - sex - prior site of care - cancer diagnosis - opioid dose - length of stay - discharged/ died	from chart review: - impaired mental status (IMS): 1 of: confusion/delusions/hallucinations/fluctuating LOC/ haloperidol prn ;2nd. period included MMSE score <24 - agitated (IMS): as above plus psychomotor agitation/severe hallucinations/regular haloperidol/other agent for delusions - haloperidol use and dose - other psychoactive drug use	chart reviewed for full duration of PCU stay	inf	0.39
Musgrave 1995	- IV intake and fluid output from chart - oral fluid intake from bedside nurse assessment - serum sodium and urea from chart	age	by patient: - thirst (none/mild/moderate/severe) by bedside nurse: - ascites - leg edema	daily, but only data within 24-48 hours of death presented	desc	0.40

Table A.9
Results of Studies Included in the Systematic Review of Published Clinical Research on
the Effects of Fluid Status or Fluid Therapy on the Dying

Study	Results	Conclusions	Comments
Burge 1993	- group's lab (mean $\pm$ SD): serum sodium = 134.5 ± 6.46 mmol/l serum osmoly = 281.1 ± 10.80 mOsm/l serum urea = 6.7 ± 2.32 mmol/l - fatigue rated worst (mean 61.8), then dry mouth, bad taste, thirst, pain, nausea (mean 24.0) - no fluid status or confounding variable was statistically significant in predicting thirst (univariate and multivariate analyses)	- fluid intake may not be "a significant determinant of distress due to thirst in those with cancer near death" - a lack of association is shown between thirst and biochemical measures of dehydration - patients report pleasure from drinking - generalizability questioned	- cross-sectional survey limitations - ie. all data at one point in time only - can VAS detect differences in thirst between patients? - fluid intake was estimate only - blinding to VAS scores not reported regarding chart review and nurse measures (possible source of detection bias) - no other methods to prevent detection bias - small sample, low power - excluded group (58% of all patients considered) differed from participant group - sicker, drinking less, needing more care, and probably more cognitively impaired; cannot generalize to > half of terminally ill - group's lab profile not very different from reference ranges; may not be wide enough to show effect?

Table A.9 (Continued)

Study	Results	Conclusions	Comments
McCann 1994	- 20 had no hunger + 11 only in first 25% of stay - 9 thirsty initially only + 12 continued until death - 31 ate/drank small amounts or nothing - all symptoms relieved with oral food/fluids, ice chips, or mouth care - symptom relief duration varied - 27 comfortable during stay and 4 had "some discomfort"	- terminally ill can experience comfort despite minimal food or fluids, as long as mouth care and sips provided - lack of fluid intake "generally produced the positive effects of decreased secretions"	- hypothesis generating study only - no comparison group - excluded patients not described - not clear how many exclusions occurred at admission versus during stay in unit (possible selection/exclusion biases) - authors played down importance of sensorium, but excluded many with impaired sensorium rather than assess its occurrence - potential role of detection bias, despite use of multiple interviewers - fluid status not assessed - validity of team consensus method not shown - conclusion re decreased secretions not supported by data presented - other statements not supported by data presented (eg. reduction in urine volume; few patients with fluid overload)

Table A.9 (Continued)

Study	Results	Conclusions	Comments
Waller 1994	- group's lab (mean $\pm$ SD): serum sodium = 141 ± 8.6 mEq/l serum osmoly = 314 ± 26.8 mOsm/kg serum urea = 142 ± 88 mg% [ref=30$\pm$15] - 87% were significantly azotemic; - 46% had hyperkalemia - worse alertness correlated with higher sodium ($p<0.001$), serum osmolality ($p<0.02$) and urine osmolality ($p<0.01$) - IV group vs. controls: serum osmolality ($p<0.02$) and sodium ($p<0.01$) higher in IV group; no significant difference in serum urea; no significant difference in alertness ($p=0.448$)	- vast majority of study patients were dehydrated near death - no correlation between IV fluid therapy and state of consciousness - IV fluids are medically unnecessary in cancer patients during the last days of life and may be detrimental - indirect support for observation that survival of terminal cancer patients is no different between settings that usually give or do not give IV fluids	- cross-sectional survey limitations - ie. all data at one point in time only - hypothesis generating design only - conclusions much too strong for the design and the evidence - demographics for subjects not given; cannot compare the 2 groups - excluded patients not enumerated or described; - potential selection bias occurred when subjects chosen and when IV use decided - no description of other treatments used - detection bias possible when assessing alertness for IV or non-IV patients - lab results not all reported and not explained - IV intervention vague - multiple statistical testing problem not addressed - no discussion of statistical power - cannot generalize the results - survival-equivalence statement inappropriate - not tested in this study

Table A.9 (Continued)

Study	Results	Conclusions	Comments
Ellershaw 1995	- group's lab (mean $\pm$ SD): serum sodium = 139.6 ± 6.7 mmol/l serum osmoly = 298.6 ± 22.3 mOsm/kg serum urea = 15.5 ± 12.9 mmol/l - at initial assessment 46 had respiratory secretions and 36 did not - no difference in biochemical parameters between these 2 groups ($p=0.134-0.838$) - no difference between hydration groups in proportions with respiratory secretions at all or persistently ($p=0.104-0.911$) - no difference between hydration groups ($p=0.532$) in proportions that could respond to symptom questions (28% of total) - thirst (83%) and dry mouth (87%) were common in all those able to respond - 79 % of lung cancer patients had initial respiratory secretions versus 49% of others ($p=0.022$); no difference in proportions with persistent secretions ($p=0.169$) - 5 of 6 with respiratory infection had secretions at initial assessment; none had persistent secretions - $>= 91\%$ of patients able to respond to questions were receiving potentially drying drugs	- high proportion of dying patients have normal biochemistry - respiratory tract secretions, thirst and dry mouth are common in the dying and not significantly related to hydration status - thirst and dry mouth "appear not to be solely related to dehydration" - respiratory tract secretions can be controlled by lyosocine hydrobromide in the majority of patients - Thirst may be related to dry mouth (hypothesis) - use of fluid therapy to relieve thirst and dry mouth "may be futile"	- limitations of design - cross-sectional for thirst, dry mouth, and lab; follow-up retrospective review for respiratory secretions, but 56% had outcome at start - hypothesis generating - selection of subjects potentially biased; eligibility determined potentially at same time respiratory secretions and clinical hydration status could be assessed - vague entry criterion of "dying" - excluded patients not enumerated or described; generalizability not clear - validity and reliability of respiratory secretions and infection outcomes not clear - validity of biochemical dehydration definition not clear - may have resulted in misclassifications? - the two cohorts likely became more similar with respect to hydration status between study entry and death - data collection after death potentially biased by knowledge of initial assessment or lab results - very low response rate to thirst/dry mouth question - multiple statistical testing problem not addressed - statistical power not addressed - conclusion regarding effectiveness of lyosocine not appropriate - not tested in this study

Table A.9 (Continued)

Study	Results	Conclusions	Comments
Bruera 1995	from 1st. to 2nd. time period: - total IMS incidence unchanged from 32% to 41% (NS) - agitated IMS decreased from 26% to 10% ($p < 0.001$) - regular haloperidol use decreased from 24% to 8% ($p < 0.01$) - daily haloperidol dose decreased from mean 5.6 mg/day to 3.6 mg/day ($p < 0.01$) - other psychoactive drug use decreased ($p < 0.01$) - hypodermoclysis use increased from 32% to 73% ($p < 0.01$) - oploid rotation occurred more often - 21% vs. 41% ($p = 0.001$)	- "relatively low volumes of water per day may help prevent the development of agitated delirium" - "not possible to establish the relative contribution of cognitive monitoring, hydration and oploid rotation in this study"	- limitations of retrospective chart reviews (adequacy and accuracy of recordings; interpretation) - natural, population-based experiment - hypothesis generating only - potential bias in outcome detection because of lack of blinding to time period - change in definition of IMS between time periods - potential for unmeasured changes to have occurred between the 2 time periods (eg, comorbidity; referral pattern; other treatments) - multiple statistical testing problem not addressed
Musgrave 1995	- 95% had thirst - 78% had edema/ascites - thirst levels compared with respect to: - IV fluid volume received - volume of fluid output - oral fluid intake - serum sodium - serum urea - presence of ascites/edema - IV volume levels compared with respect to presence of ascites/edema - no obvious pattern noted in any of these descriptive comparisons - average age decreased as thirst increased	- "thirst did not appear to be greatly influenced by the quantity of IV fluids received" - "little correlation between sodium levels and the degree of thirst" - "Little relationship was found between the amount of IV fluids received and the prevalence of fluid retention signs" - due to small size, results "treated with caution"	- cross-sectional results presented, despite cohort initial design - no comparison group - hypothesis generating - demographics for group not given - half of original sample excluded - potential selection/exclusion bias - other treatments or conditions not included - may have affected outcomes - possibility of detection bias regarding presence of ascites/edema if thirst levels/IV volumes known (not blinded) - small sample size with missing data as well (only 12 out of 19 had lab results); resulting numbers in different levels very small

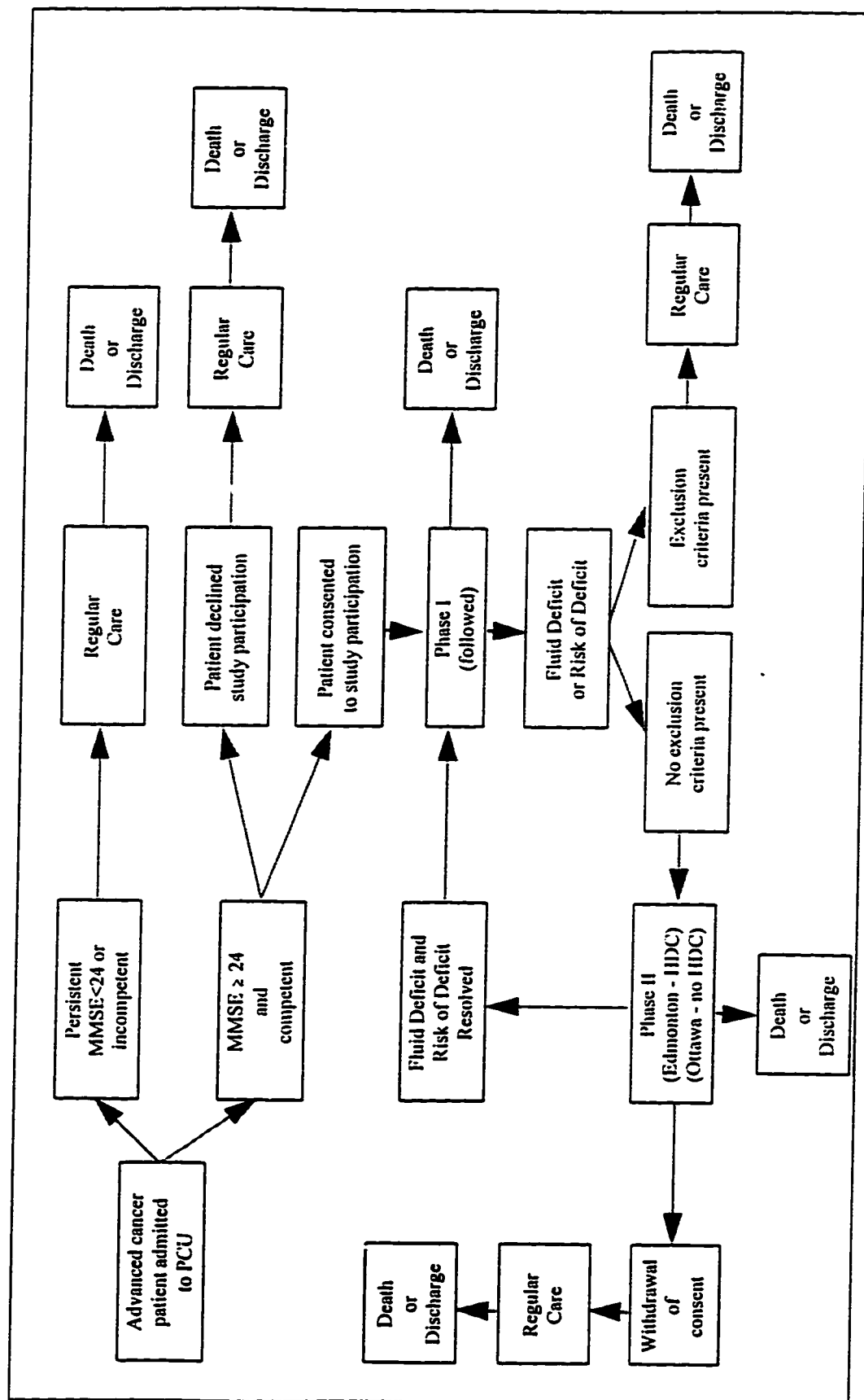
APPENDIX B

FLUID STATUS STUDY TABLES AND FIGURES

Table B.1
Comparison of the Palliative Care Units (PCUs) in Ottawa
and Edmonton by Annual Statistics and Admission Criteria

Characteristic	Ottawa PCU	Edmonton PCU
Number of Beds	25	14
Approximate Mean Length of Stay (Days)	27	37
Discharge Rate	≤10%	≤10%
Admission Criteria	- cancer or non-cancer diagnosis - terminal care or symptom control or respite	- cancer diagnosis - difficult physical and psychosocial problems

Figure B.1
Flow diagram showing possible paths of patients considered for the Fluid Volume Status Study



PCU = Palliative Care Unit
MMSE = Mini-Mental Status Examination
IIDC = Hypodermoclysis

Table B.2
Opioid Equivalent Doses Used for Dose Conversions

Opioid	Parenteral Dose (mg)	Oral Dose (mg)
Morphine	10	20
Hydormorphone	2	4
Codeine	120	200
Diamorphine	7	14
Methadone	10	20
Anileridine	25	50

Table B.3
Pressure Ulcer Staging System

Stage	Description
1	Non-blanchable erythema of intact skin.
2	Partial thickness skin loss, involving epidermis, dermis, or both.
3	Full thickness skin loss, extending into sub- cutaneous tissue.
4	Deep, full thickness skin breakdown with complete loss of epidermis, dermis, and subcutaneous tissue and possibly extending into muscle, bone and joint.

Figure B.2
Reasons for Patients Being at Risk of Developing a Fluid Deficit on Entry to Phase II

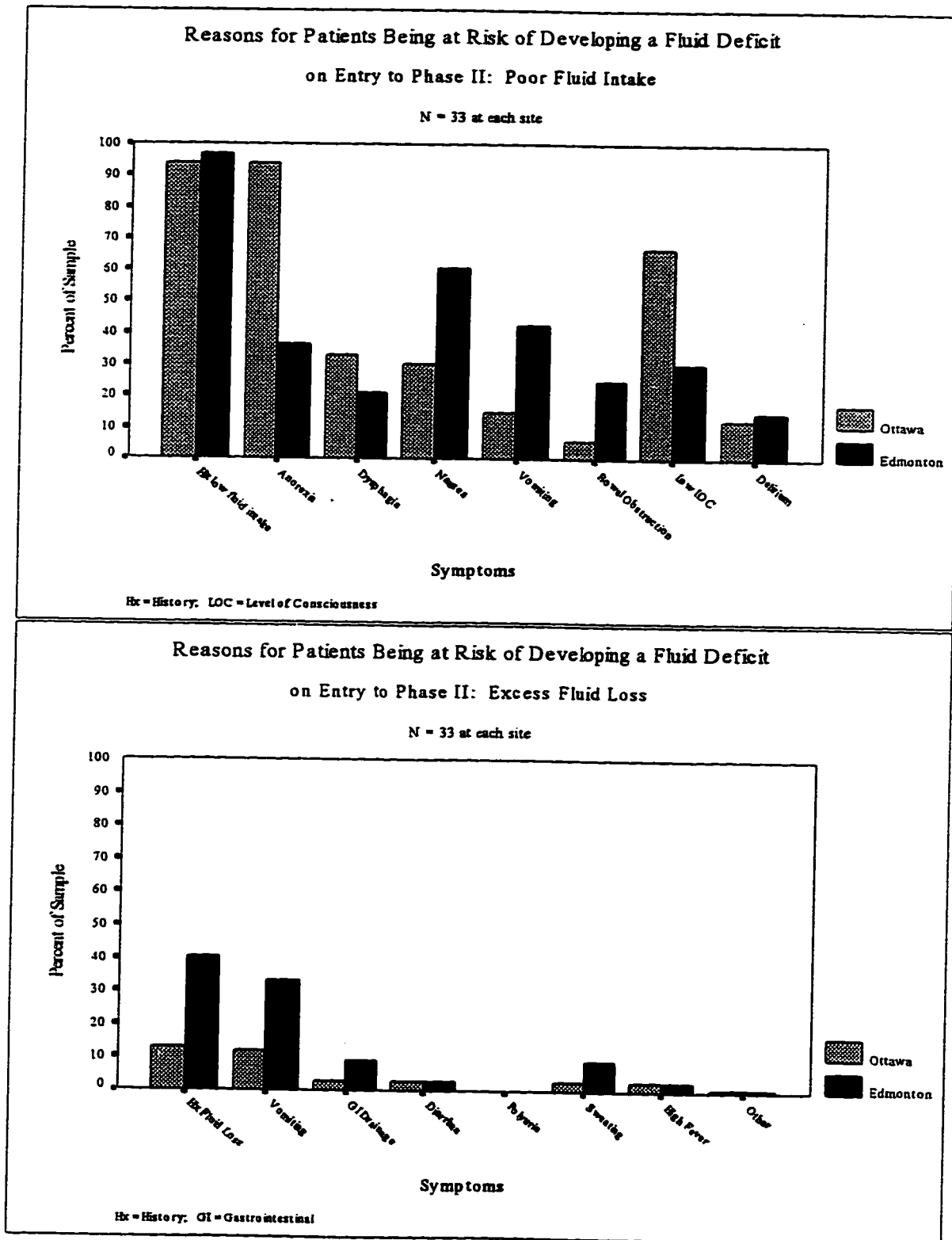


Figure B.3 Patients with a Clinical Diagnosis of Fluid Deficit at Phase II Entry

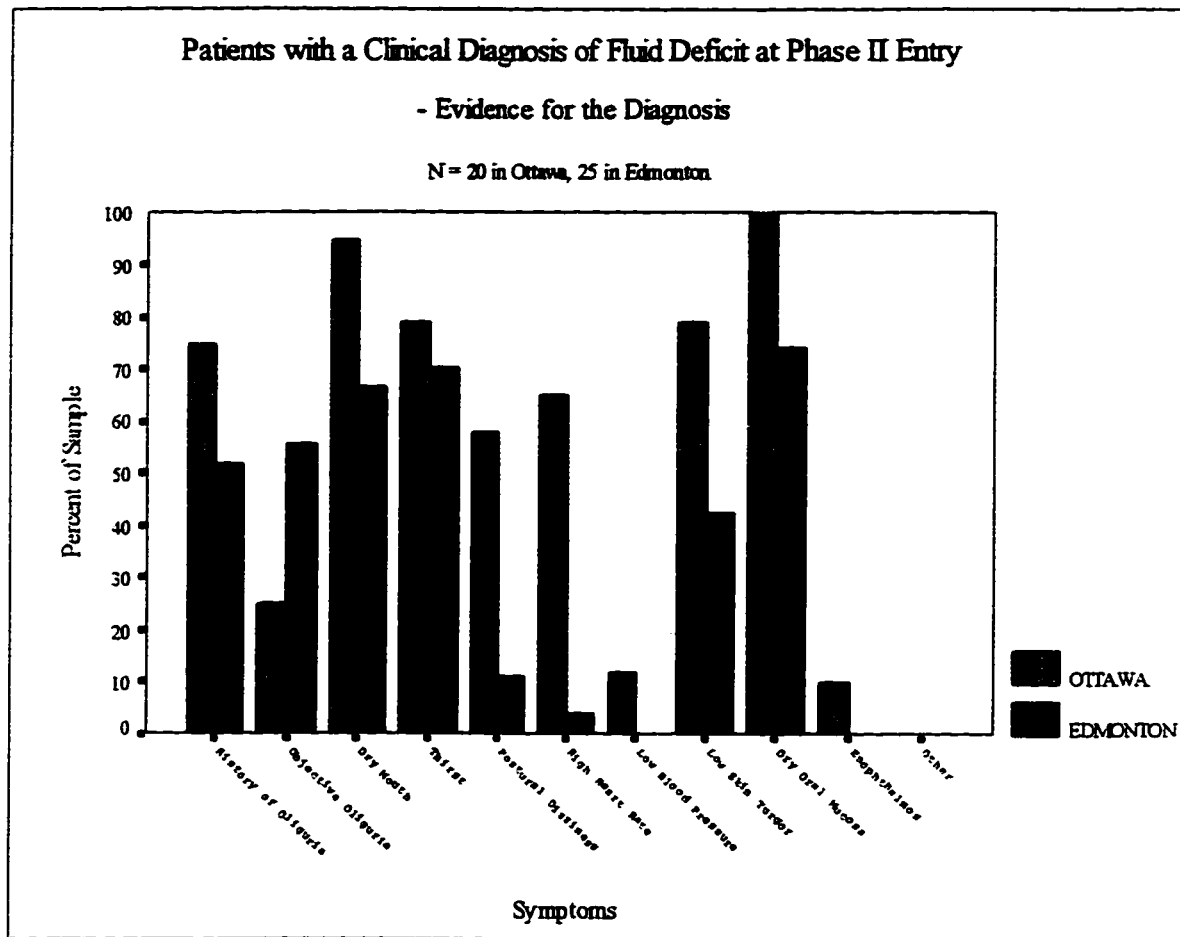


Table B.4
Forward Data Sample Sizes Remaining in Phase II
at Selected Times

Day Number	Ottawa Sample Size	Edmonton Sample Size
0	33	33
1	33	33
2	30	31
3	24	30
4	22	30
5	16	30
6	15	29
7	15	29
8	13	29
9	13	29
10	13	29
11	12	27
12	10	25
13	9	23
14	9	22
21	8	18
55	1	5
80	0	1

All data pertain to first evaluable Phase II stays only

Figure B.4 24-hour Fluid Balance

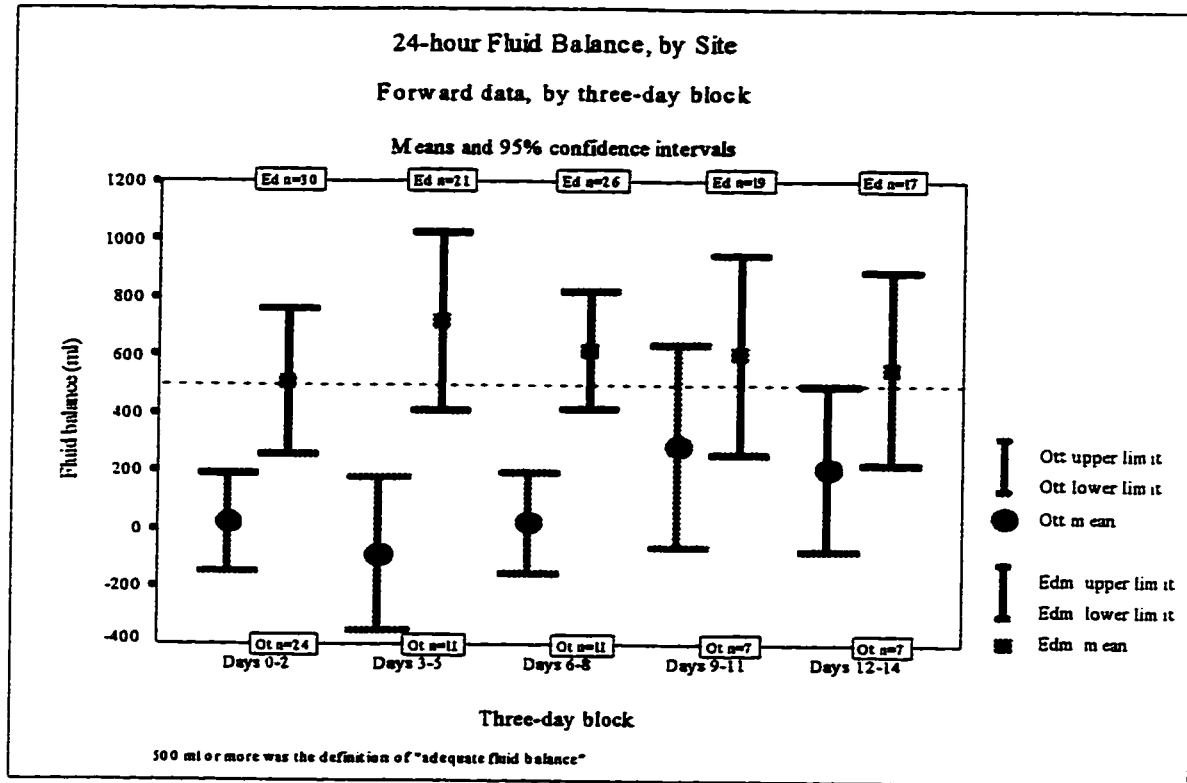


Figure B.5 24-hour Fluid Balance

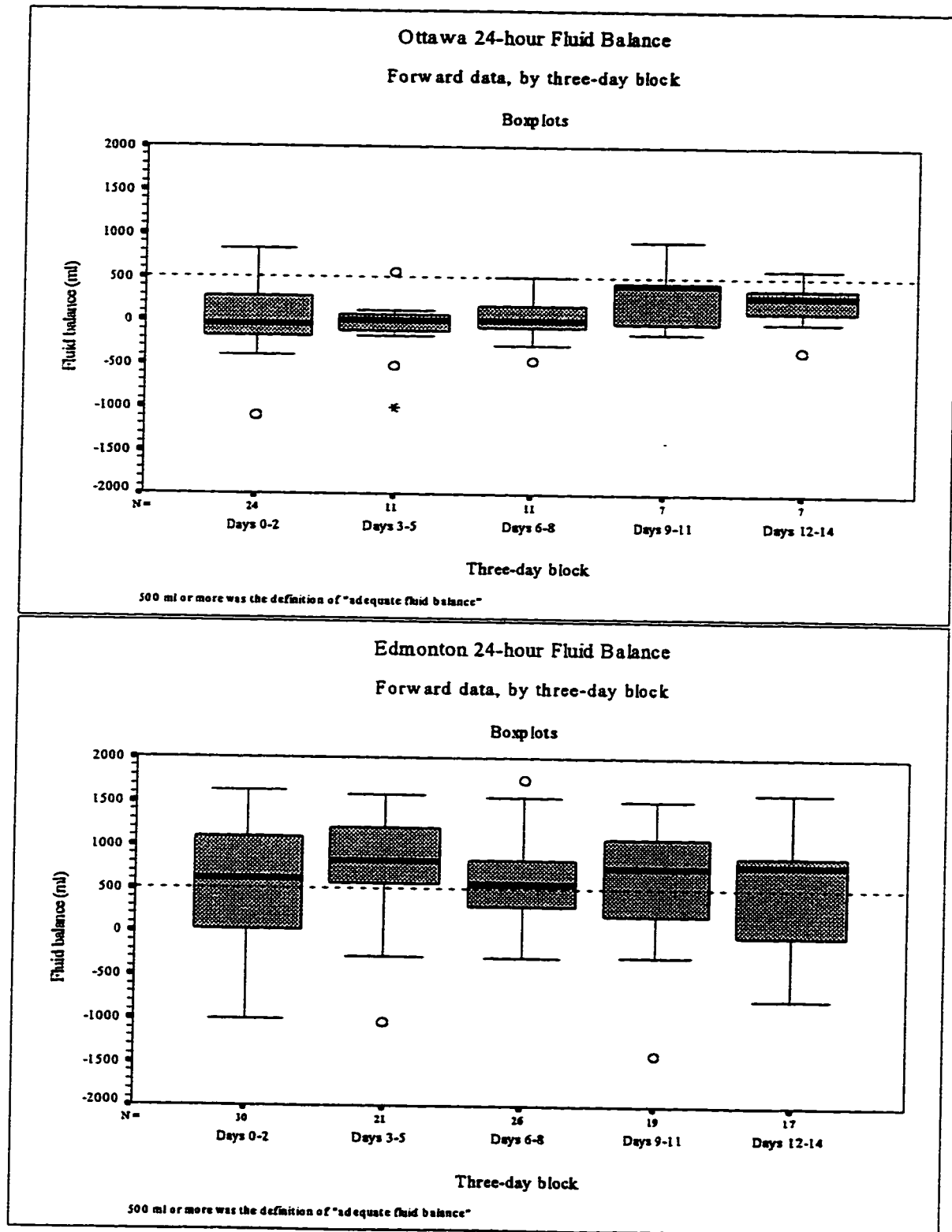


Figure B.6 24-hour Urine Output

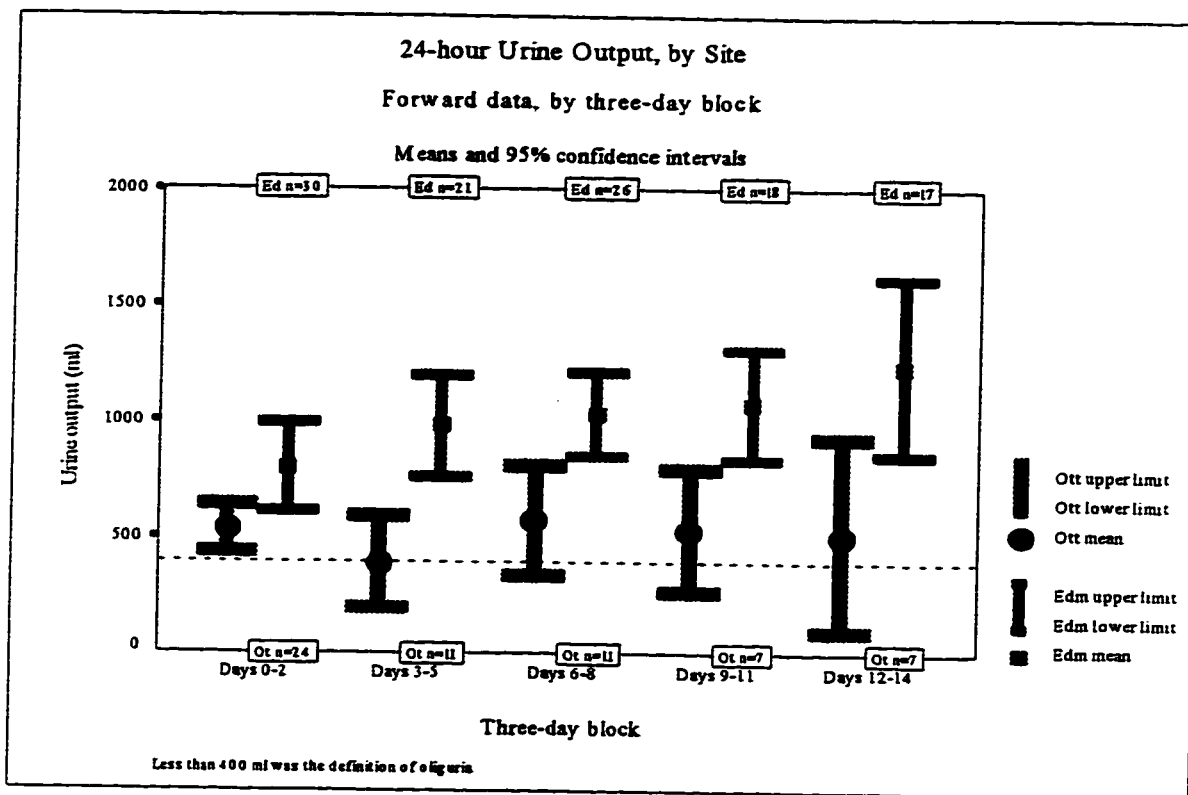


Figure B.7 24-hour Urine Output

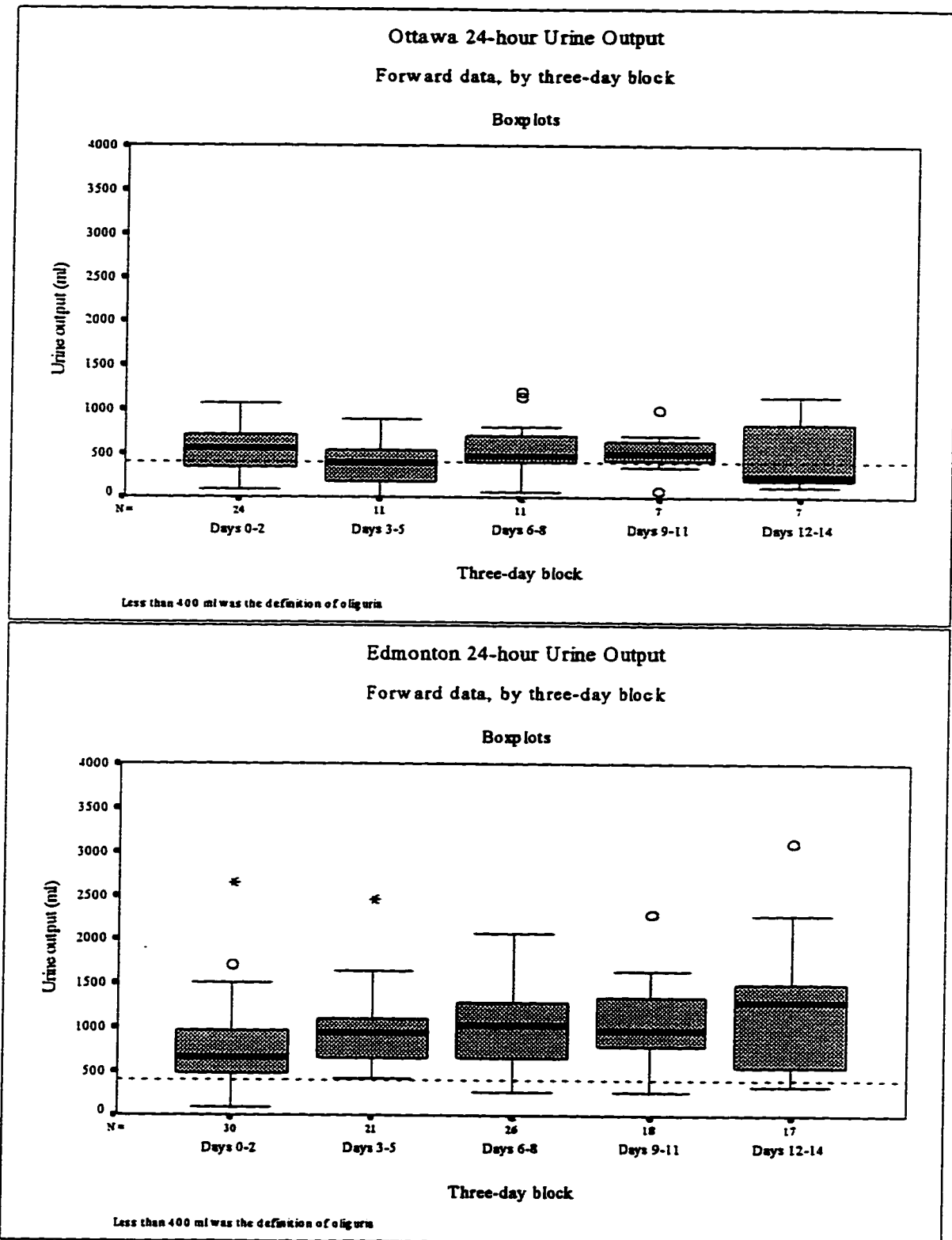


Figure B.8 Serum Urea-Creatinine Ratio

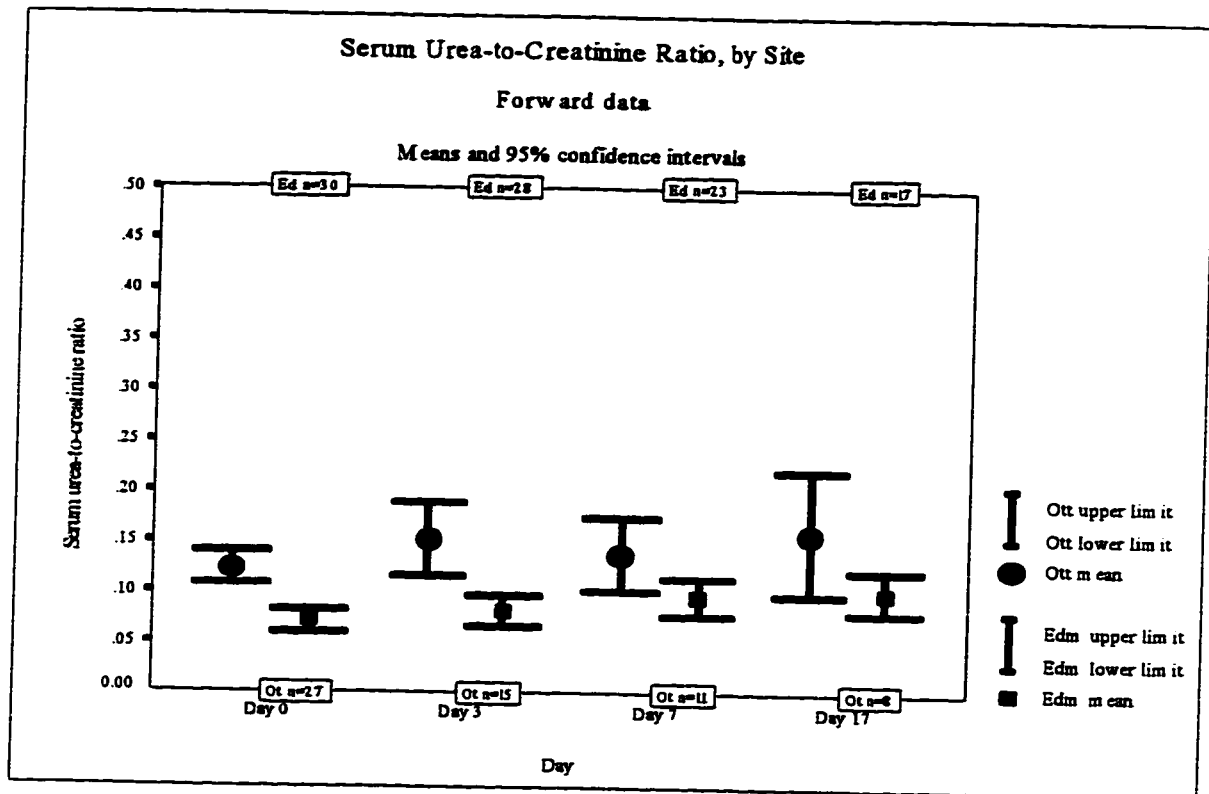


Figure B.9 Serum Urea-Creatinine Ratio

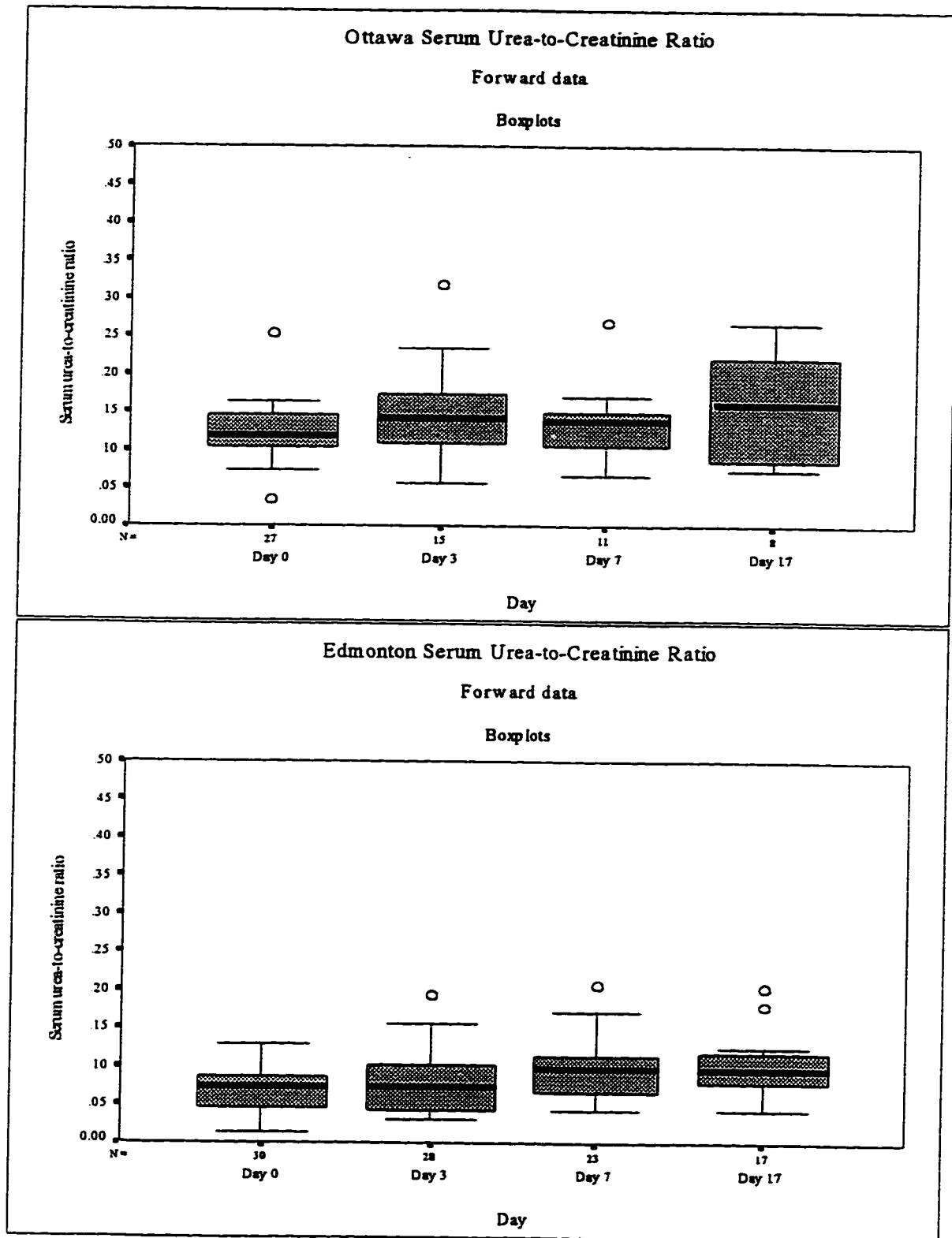


Figure B.10 Level of Consciousness

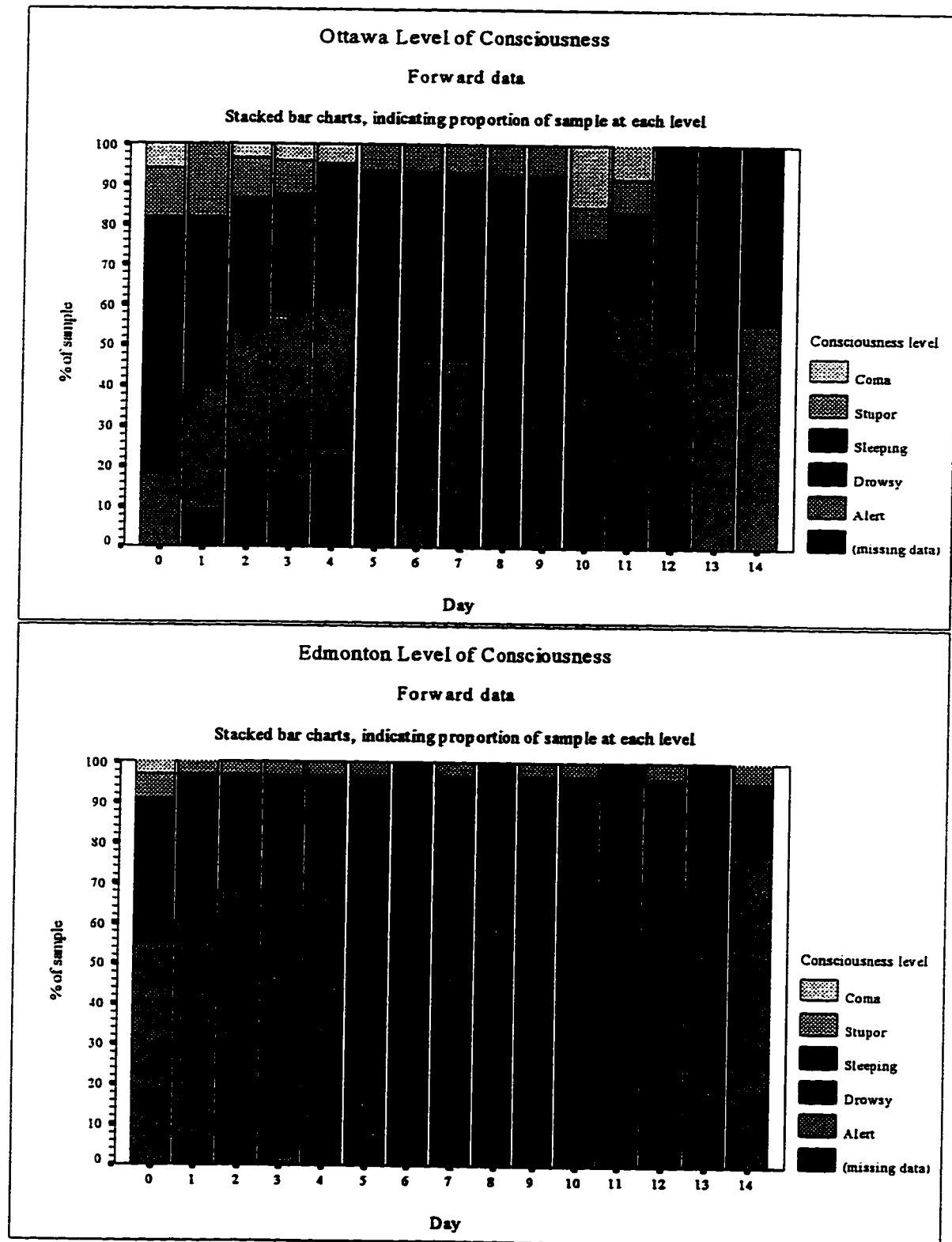


Figure B.11 Mini-Mental Status Examination Score

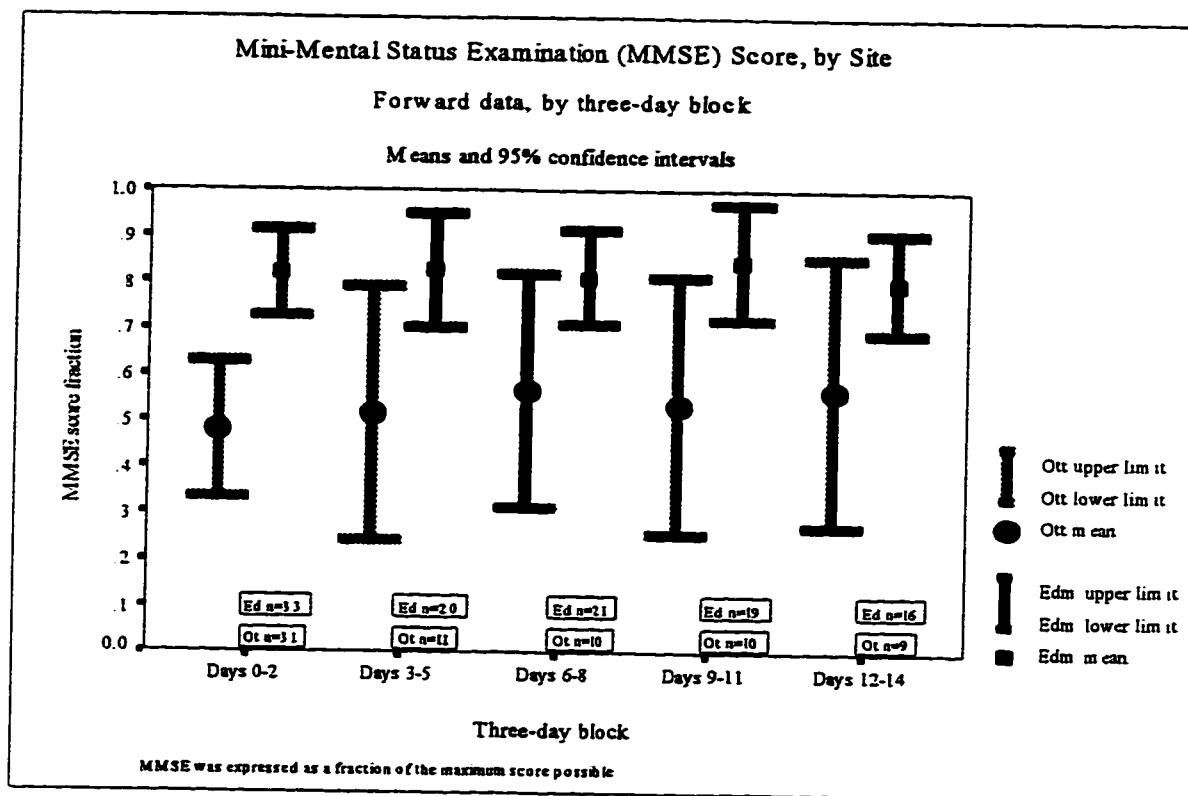


Figure B.12 Mini-Mental Status Examination Score

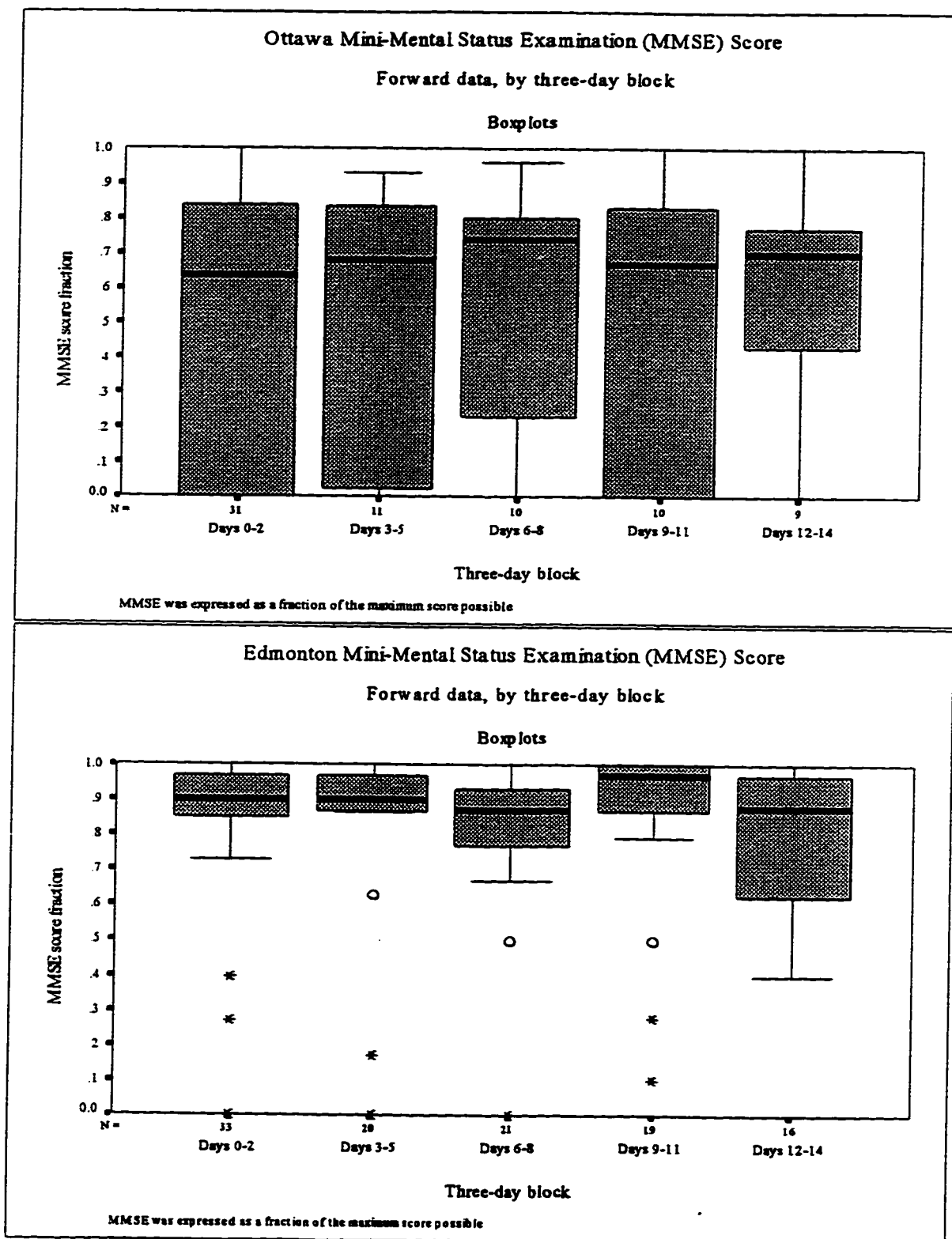


Figure B.13 Delirium Rating Scale Score

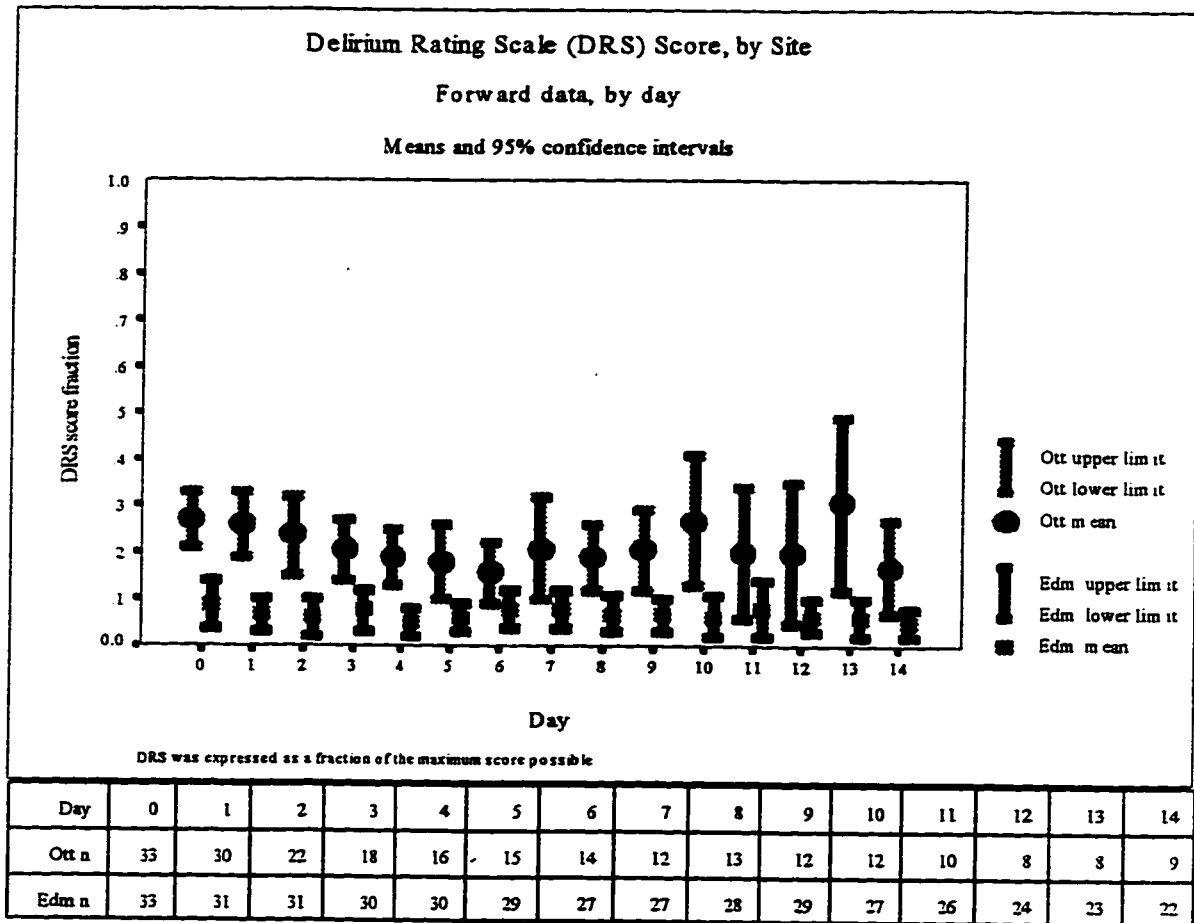


Figure B.14 Delirium Rating Scale Score

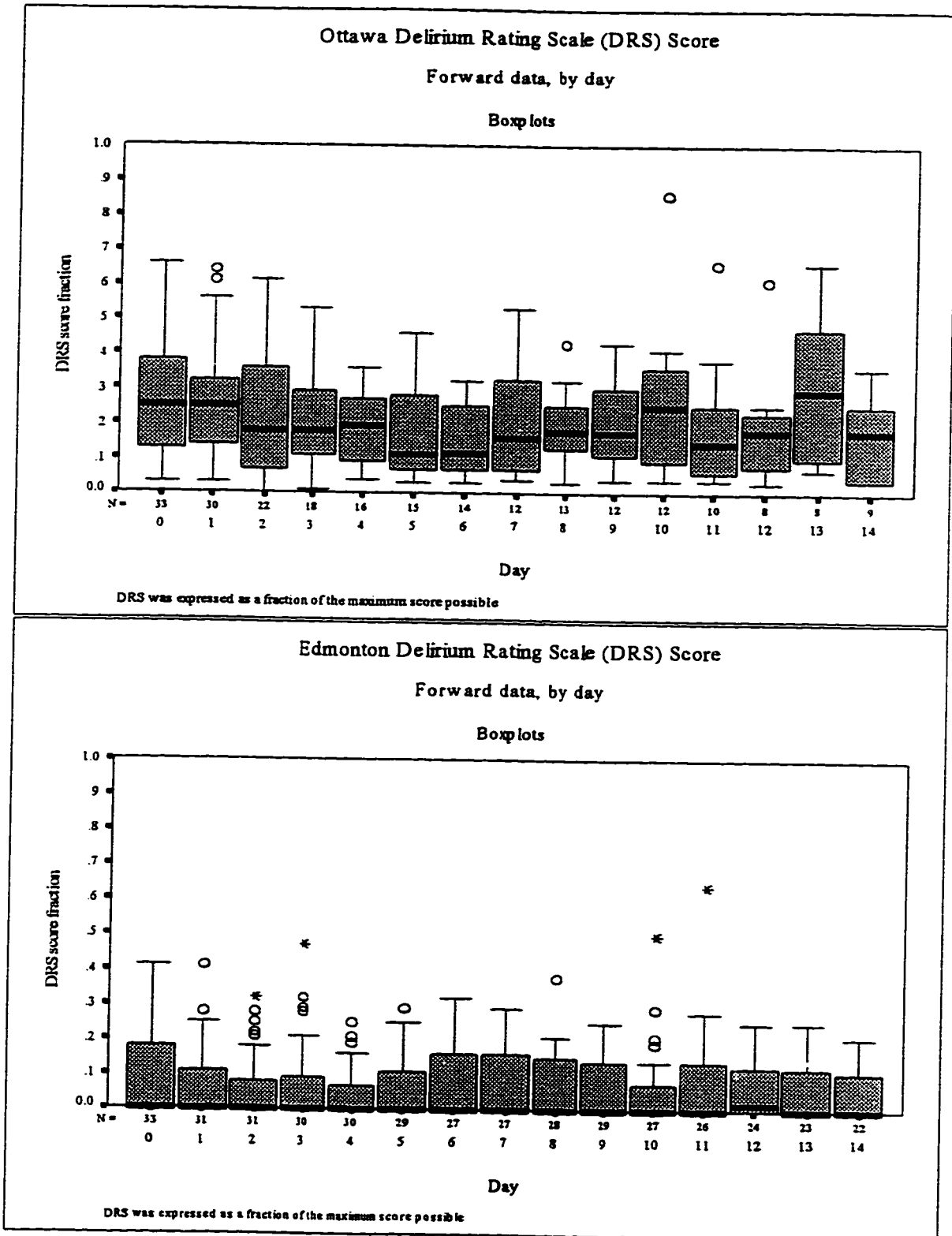


Table B.5
100 mm Visual Analogue Scale (VAS) Score for Ottawa
Forward Data for Days 0, 7 and 14
Means (SD)

VAS Item	Day 0		Day 7		Day 14	
	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Pain	21.3 (22.6) n=30	18.8 (18.0) n=21	17.1 (24.5) n=12	21.9 (25.8) n=8	21.3 (18.1) n=8	29.4 (27.2) n=8
Activity	86.7 (17.5) n=30	76.1 (29.1) n=22	85.8 (18.4) n=12	60.6 (42.5) n=8	83.1 (19.6) n=8	50.6 (31.3) n=8
Nausea	21.5 (33.2) n=30	13.1 (18.8) n=21	12.9 (20.2) n=12	8.1 (17.1) n=8	16.3 (34.3) n=8	21.3 (40.2) n=8
Depression	36.4 (28.4) n=18	43.2 (34.2) n=14	37.9 (33.9) n=7	48.3 (38.2) n=6	14.0 (14.7) n=5	18.3 (21.6) n=6
Anxiety	43.2 (29.7) n=19	34.4 (25.7) n=16	34.4 (34.3) n=8	50.0 (40.2) n=6	19.2 (28.4) n=6	27.5 (34.5) n=6
Drowsiness	70.0 (35.3) n=28	63.8 (31.9) n=21	65.4 (30.5) n=12	54.4 (37.9) n=8	65.0 (36.0) n=8	48.6 (28.4) n=7
Appetite	80.5 (30.8) n=29	78.1 (26.4) n=21	86.7 (19.7) n=12	73.8 (26.4) n=8	66.9 (41.1) n=8	94.4 (6.8) n=8
Wellbeing	60.3 (26.2) n=16	63.6 (27.3) n=14	55.7 (27.0) n=7	50.8 (13.2) n=6	43.8 (19.3) n=4	80.0 (21.4) n=6
Dyspnea	28.1 (34.5) n=29	17.0 (24.0) n=22	22.5 (23.9) n=12	27.5 (38.1) n=8	11.9 (15.3) n=8	12.9 (24.8) n=7
Weakness	82.4 (19.5) n=27	74.0 (25.9) n=20	77.7 (30.2) n=11	72.5 (18.9) n=8	75.0 (30.1) n=8	53.0 (17.5) n=5
Thirst	49.4 (35.0) n=26	46.2 (31.2) n=21	32.7 (24.7) n=11	55.0 (28.3) n=7	67.9 (27.2) n=7	61.2 (13.1) n=4
Dry Mouth	57.8 (27.5) n=29	52.8 (30.3) n=20	48.2 (25.0) n=11	38.6 (30.1) n=7	66.4 (21.9) n=7	57.5 (15.0) n=4

Table B.6
100 mm Visual Analogue Scale (VAS) Score for Edmonton
Forward Data for Days 0, 7 and 14
Means (SD)

VAS Item	Day 0		Day 7		Day 14	
	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Pain	23.1 (20.0) n=29	25.9 (20.8) n=31	22.8 (18.3) n=26	22.2 (19.8) n=27	23.4 (17.0) n=20	20.0 (15.3) n=20
Activity	71.3 (24.0) n=29	73.1 (26.7) n=31	64.4 (28.5) n=26	76.0 (23.2) n=27	64.1 (28.2) n=20	65.4 (26.6) n=20
Nausea	27.1 (28.9) n=29	31.2 (34.5) n=31	19.8 (21.6) n=26	16.9 (20.0) n=27	12.3 (6.0) n=20	23.8 (30.5) n=20
Depression	34.8 (25.9) n=28	29.3 (27.8) n=31	39.8 (27.9) n=26	32.2 (29.8) n=27	23.7 (15.0) n=20	26.3 (27.3) n=20
Anxiety	27.4 (24.5) n=28	25.7 (25.0) n=31	30.0 (23.1) n=26	25.4 (21.6) n=27	23.8 (17.9) n=20	17.0 (19.0) n=20
Drowsiness	59.3 (29.2) n=29	56.1 (36.2) n=31	49.2 (27.4) n=26	51.9 (27.9) n=27	48.2 (30.2) n=20	30.0 (28.7) n=20
Appetite	73.5 (28.9) n=29	74.7 (29.8) n=31	59.2 (30.1) n=25	63.1 (29.5) n=26	57.3 (30.0) n=20	67.6 (32.1) n=20
Wellbeing	61.5 (26.4) n=29	58.7 (30.0) n=30	56.5 (30.6) n=26	47.3 (27.0) n=26	44.3 (26.2) n=20	52.5 (26.4) n=20
Dyspnea	28.6 (25.9) n=29	23.2 (22.7) n=31	27.3 (25.5) n=26	27.1 (28.9) n=27	29.7 (22.4) n=20	20.9 (24.0) n=20
Weakness	52.8 (35.1) n=21	46.2 (37.9) n=22	51.4 (31.5) n=21	47.2 (36.1) n=22	47.3 (25.2) n=17	57.9 (29.4) n=18
Thirst	34.8 (33.9) n=21	29.1 (34.4) n=24	37.4 (28.2) n=21	29.5 (28.6) n=22	29.8 (26.1) n=17	47.4 (32.4) n=18
Dry Mouth	51.9 (32.0) n=21	41.5 (39.7) n=24	44.1 (28.5) n=21	29.7 (28.1) n=22	43.7 (29.2) n=17	36.4 (33.7) n=18

Figure B.15 Percentage of Visual Analogue Scales Completed by Staff

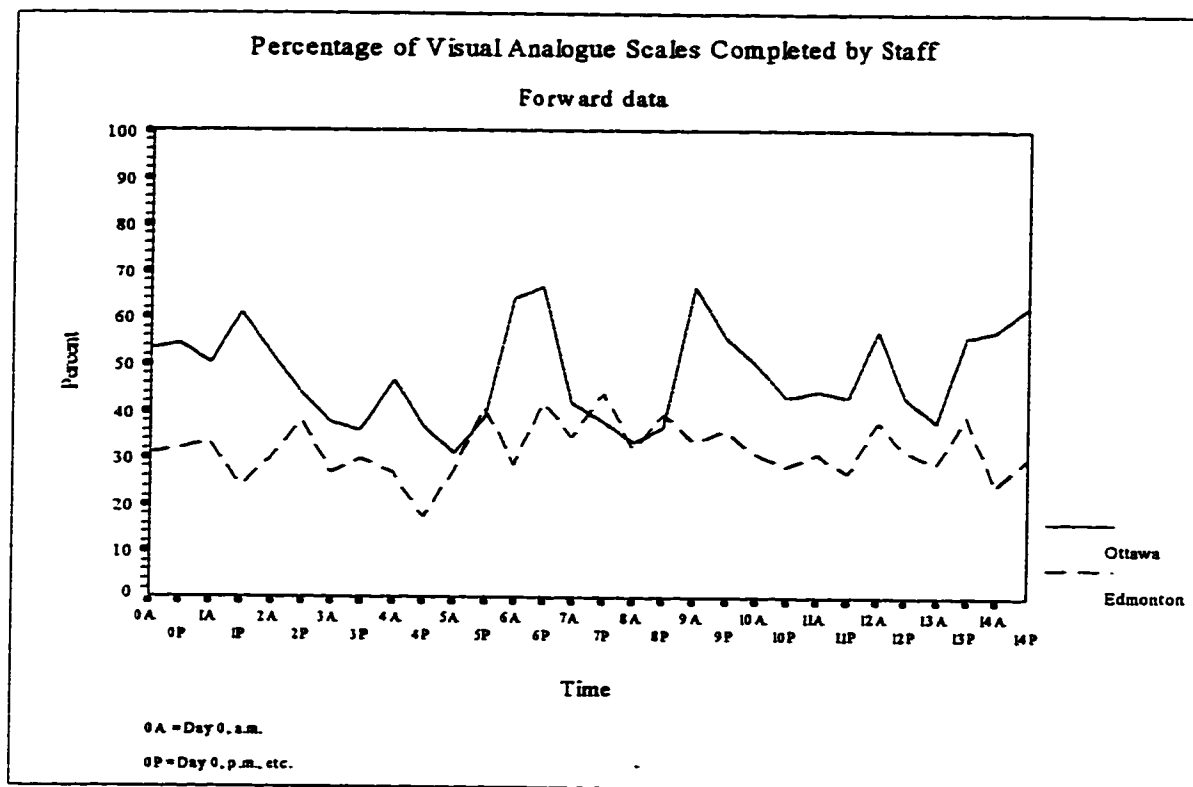


Figure B.16 24-hour Oral Morphine-Equivalent Dose

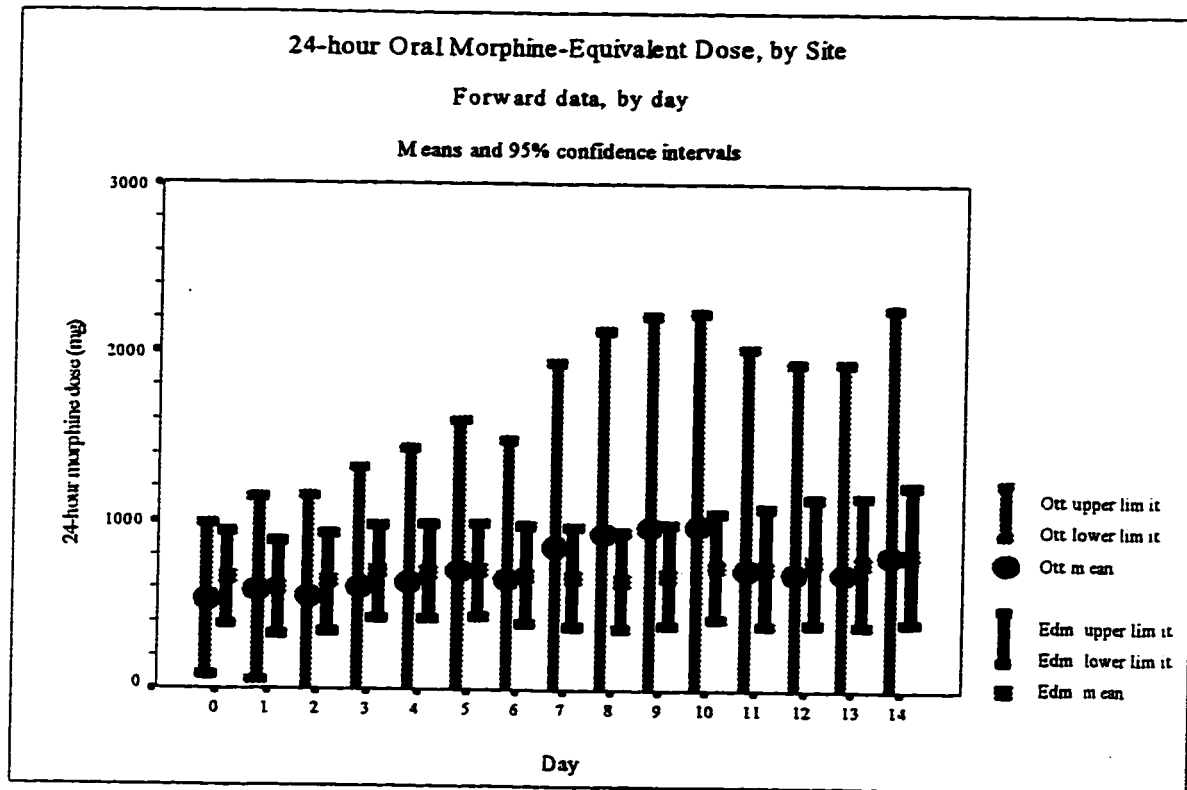


Figure B.17 24-hour Oral Morphine-Equivalent Dose

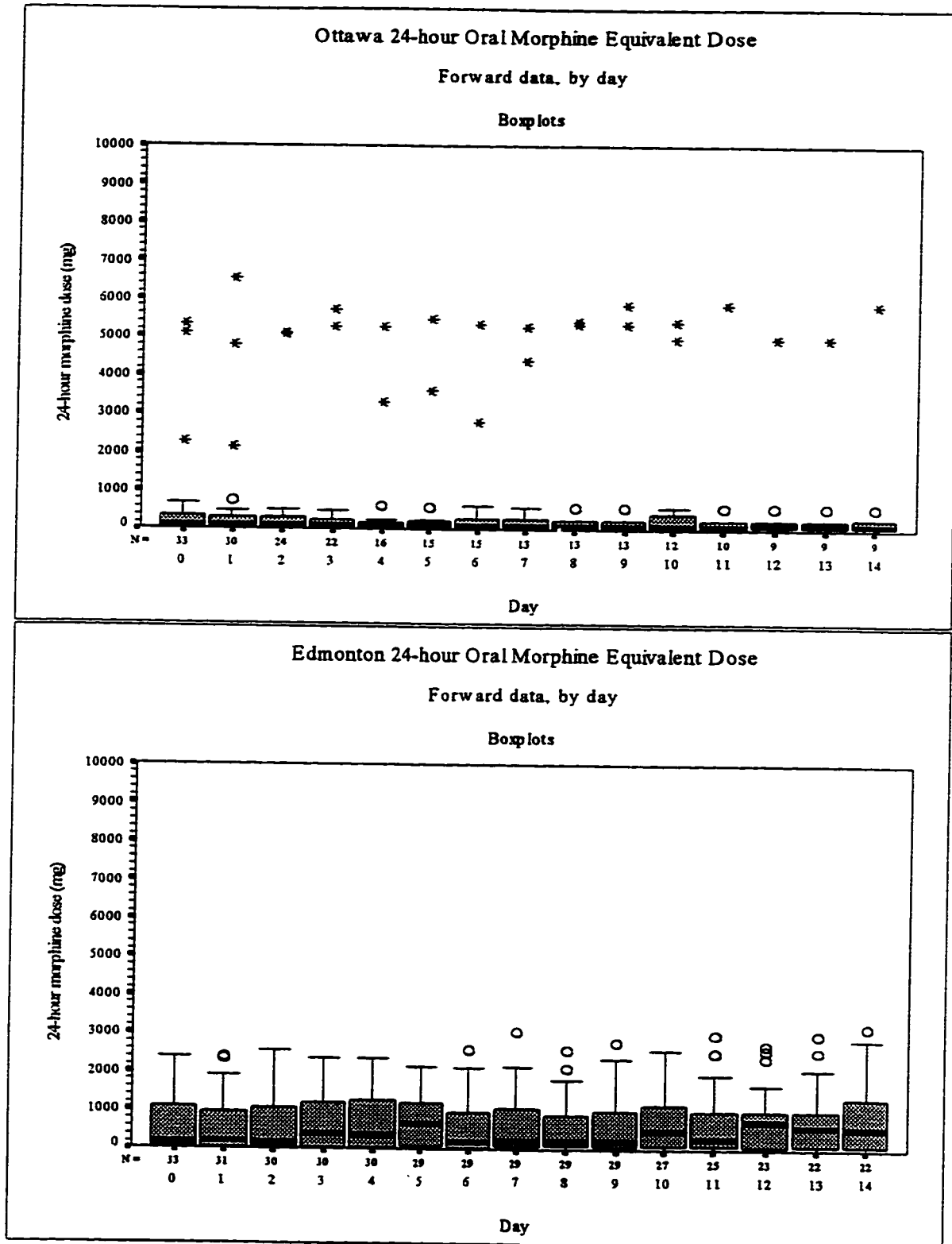


Figure B.18 Sedating Agent Use

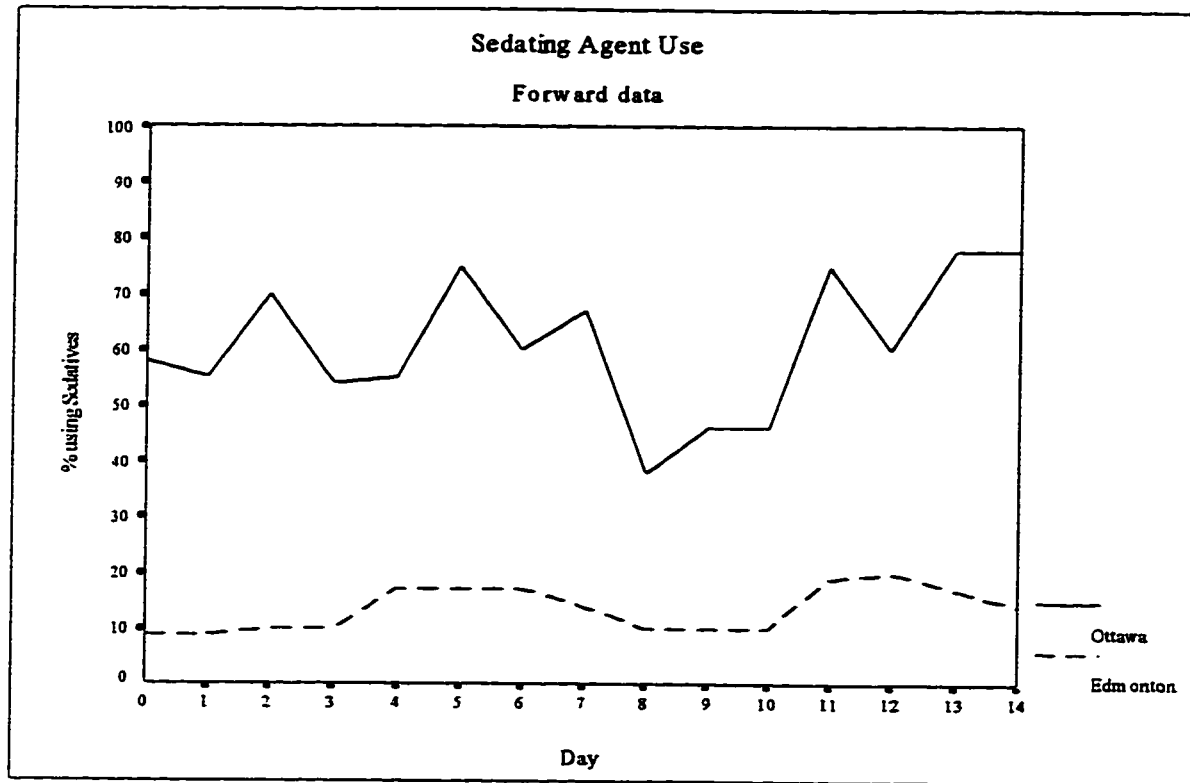


Figure B.19 Laxative Agent Use

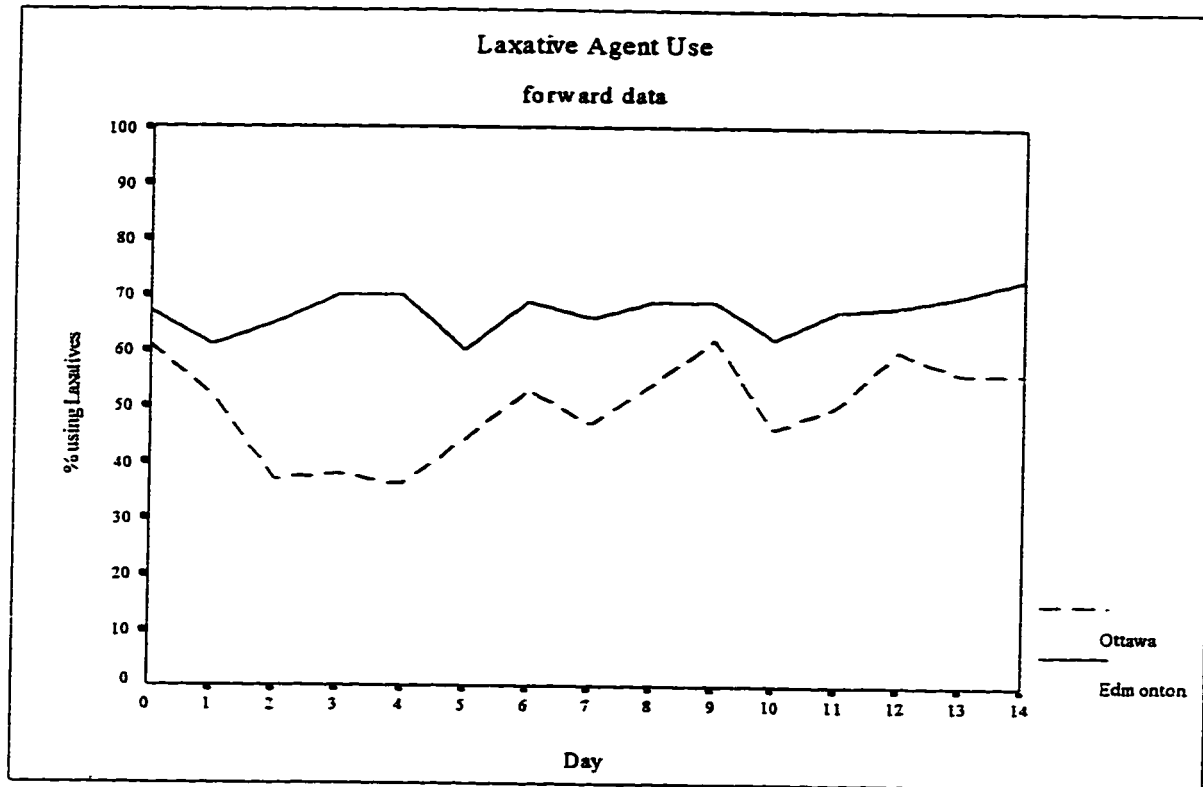


Table B.7
Reverse-Order Data Sample Sizes Remaining in Phase II
at Selected Times

Days Prior to Death	Ottawa Sample Size	Edmonton Sample Size
0 (Day of Death)	33	27
1	30	25
2	24	25
3	22	25
4	16	25
5	15	24
6	15	24
7	13	24
8	13	24
9	13	24
10	12	22
11	10	21
12	9	20
13	9	19
14	8	19

Figure B.20 24-hour Fluid Balance

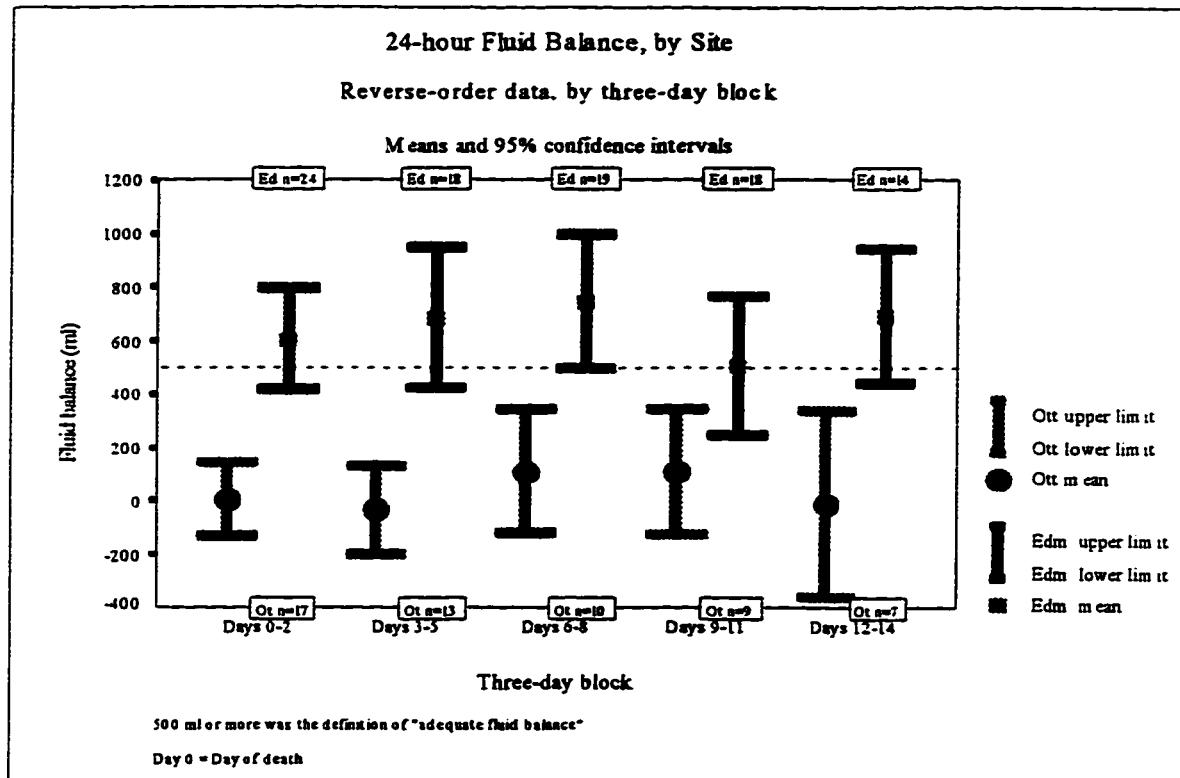


Figure B.21 24-hour Fluid Balance

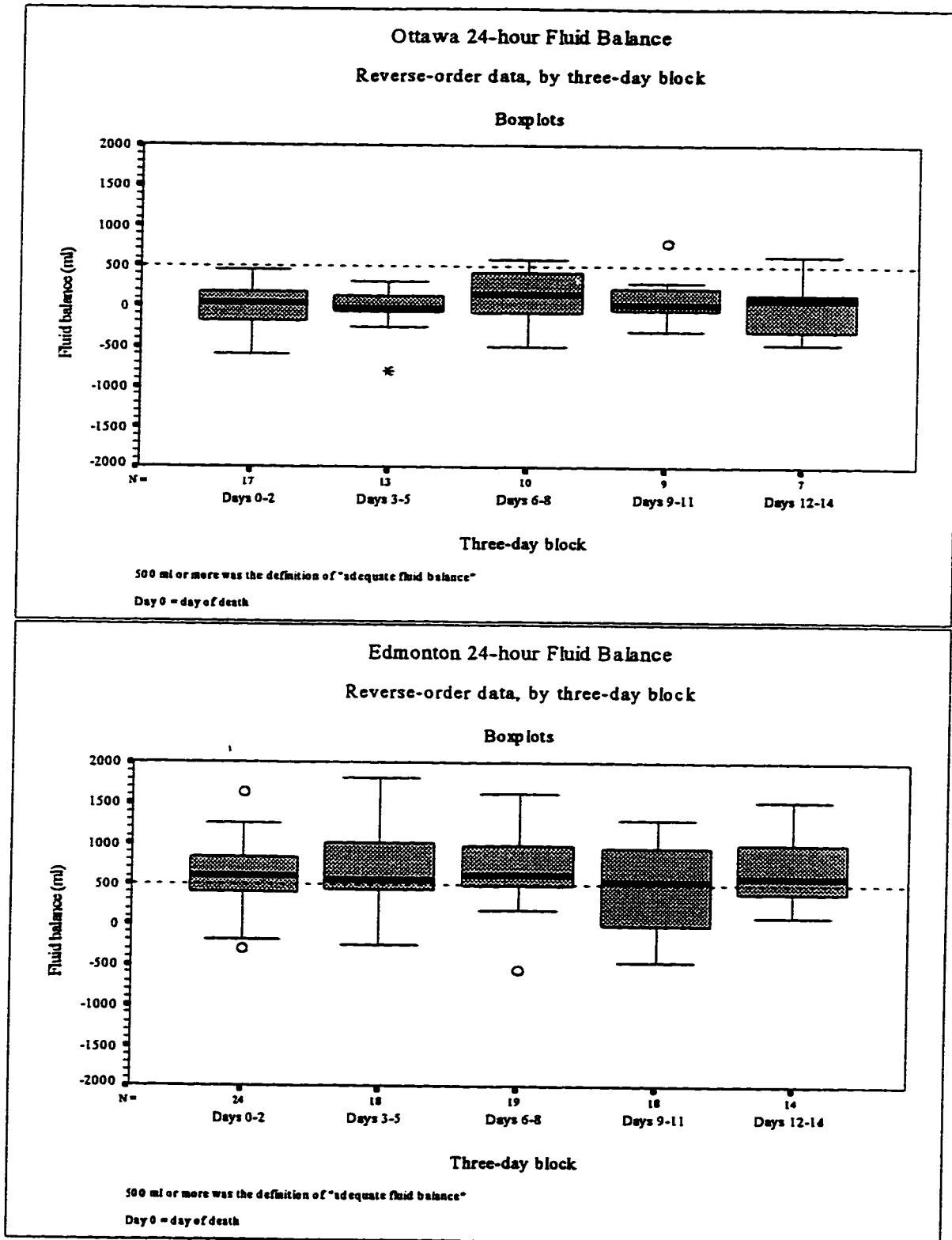


Figure B.22 24-hour Urine Output

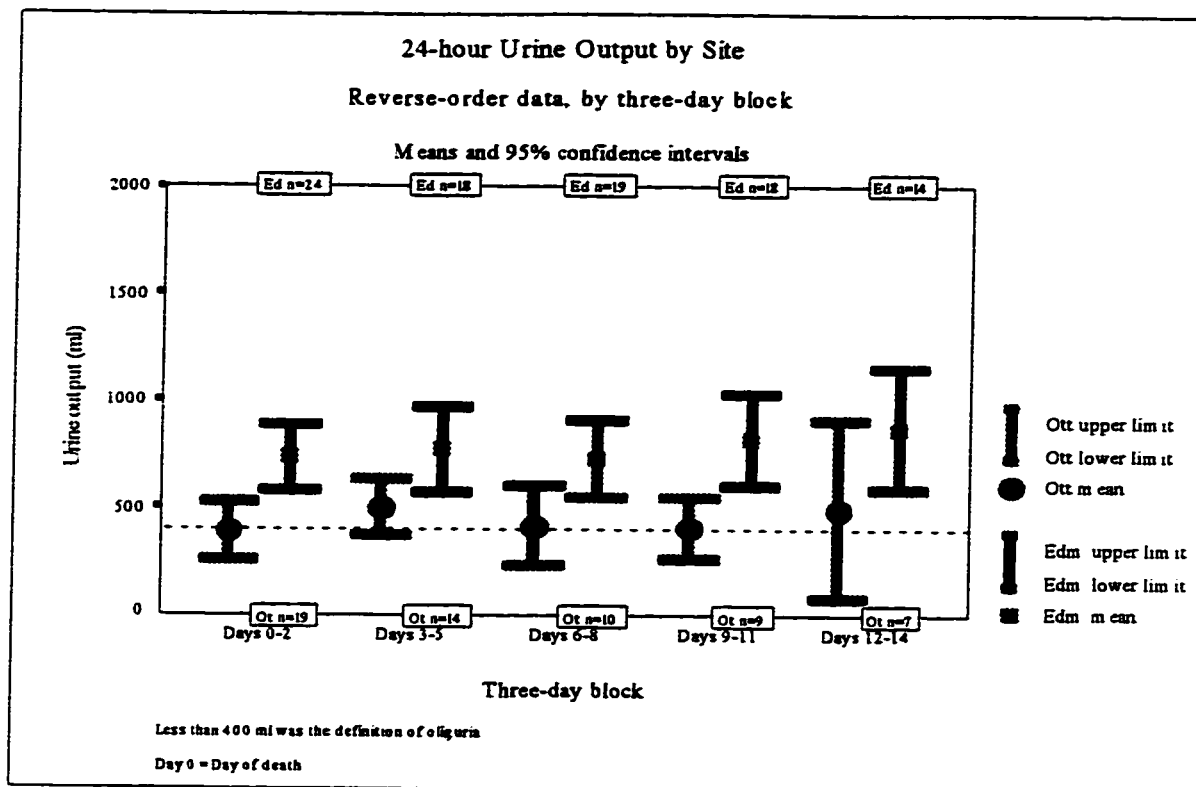


Figure B.23 24-hour Urine Output

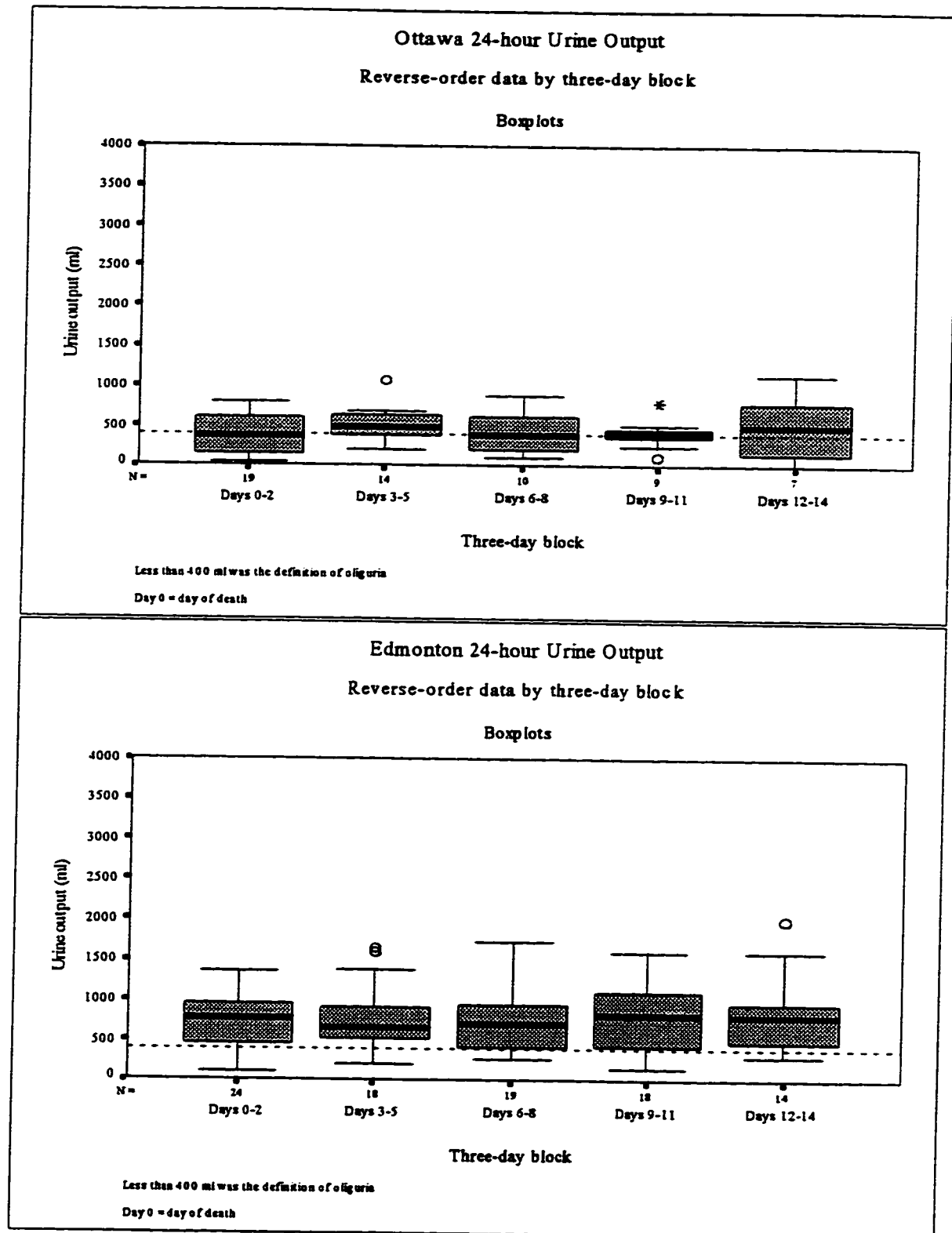


Figure B.24 Serum Urea-Creatinine Ratios

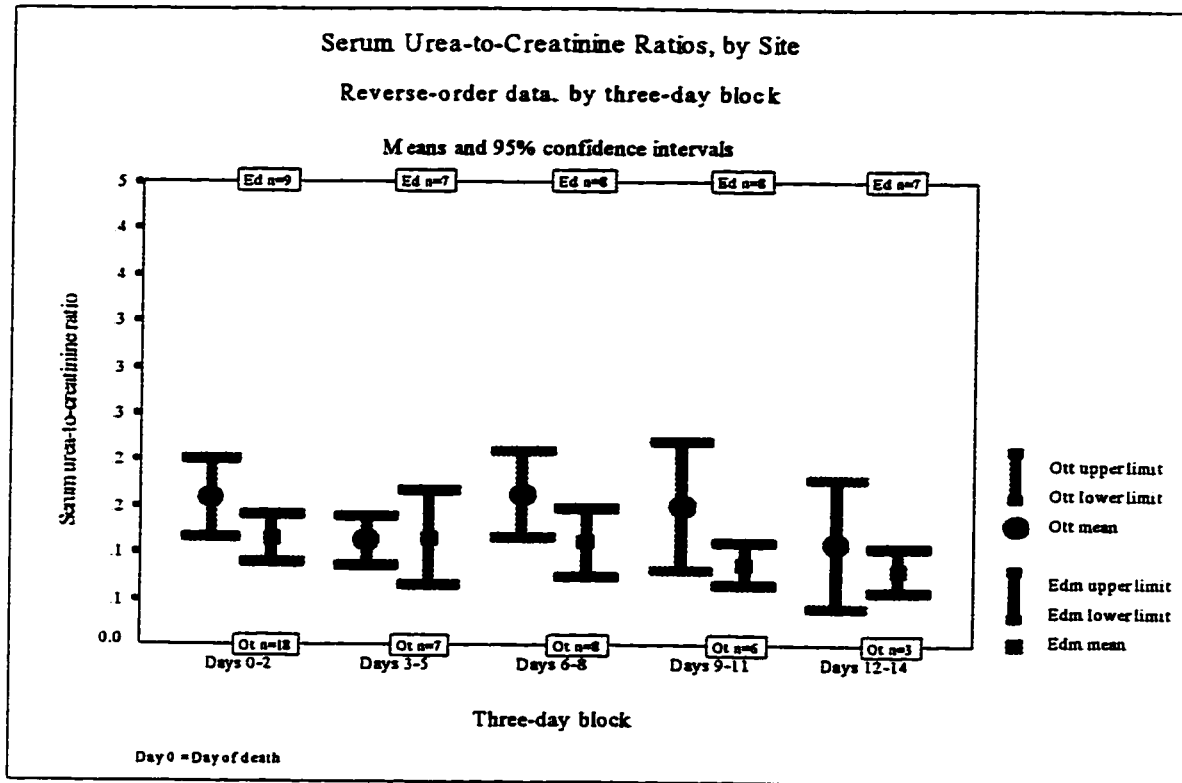


Figure B.25 Serum Urea-Creatinine Ratio

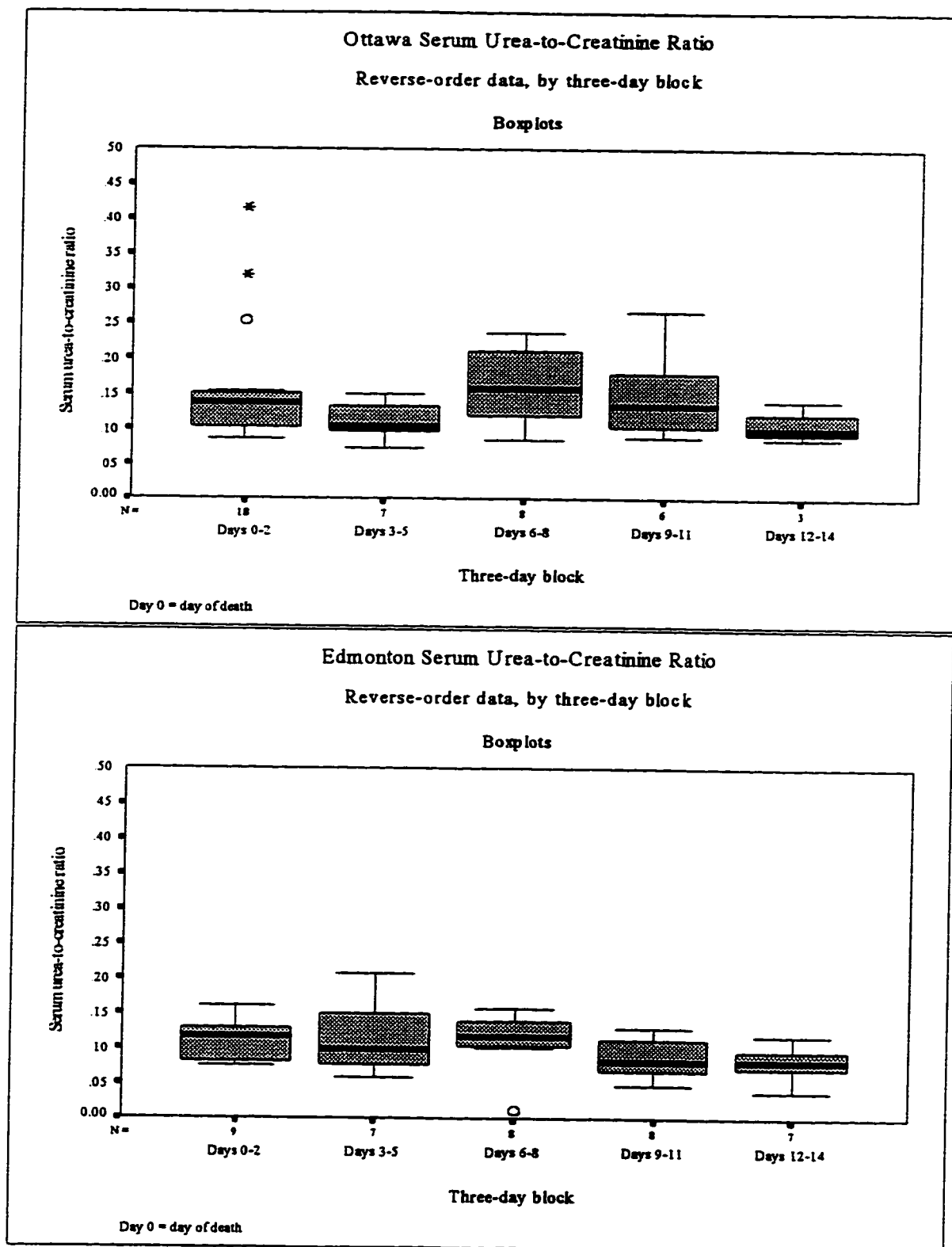


Figure B.26 Level of Consciousness

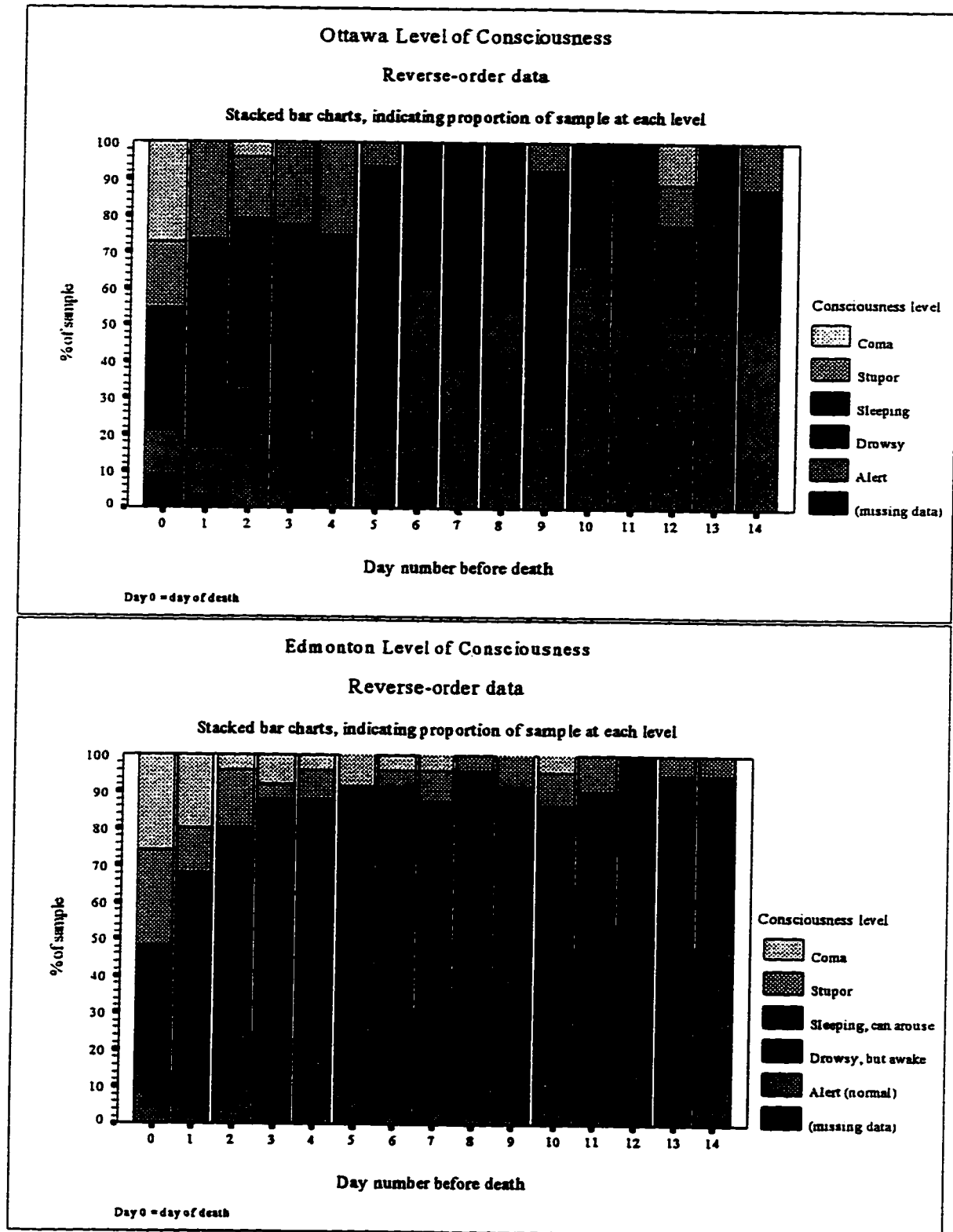


Figure B.27 Mini-Mental Status Examination Score

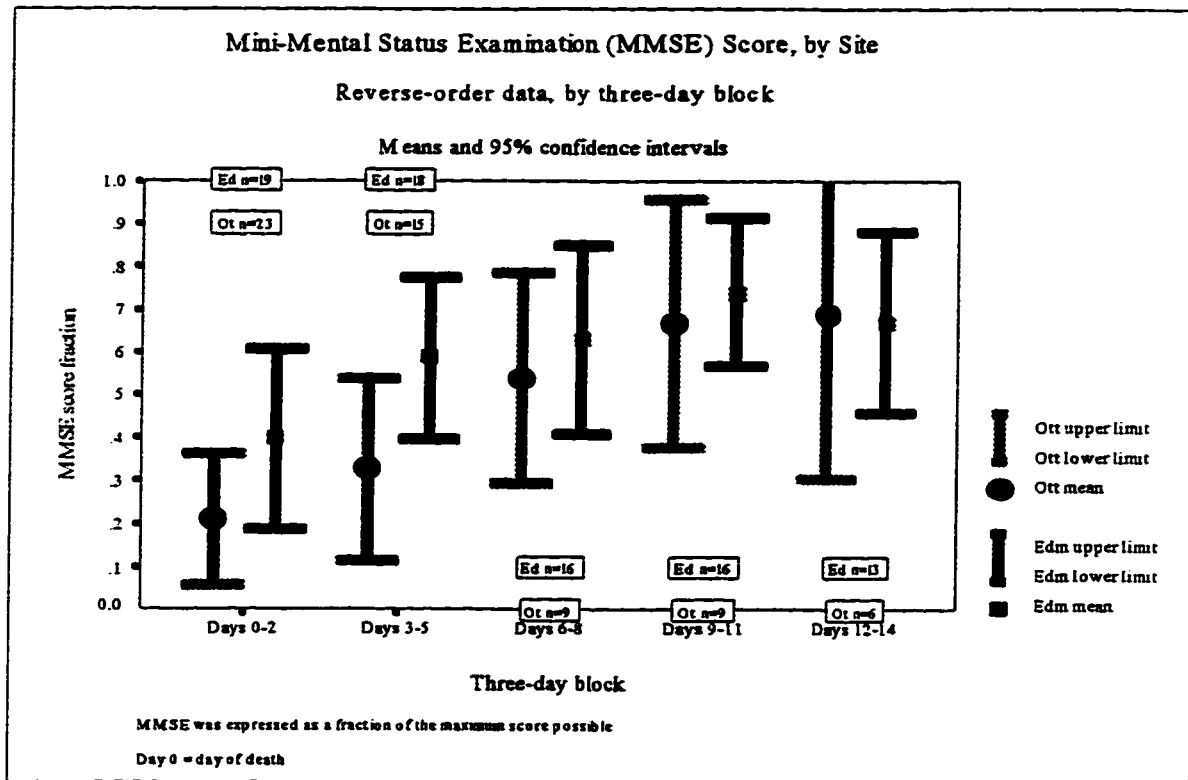


Figure B.28 Mini-Mental Status Examination Score

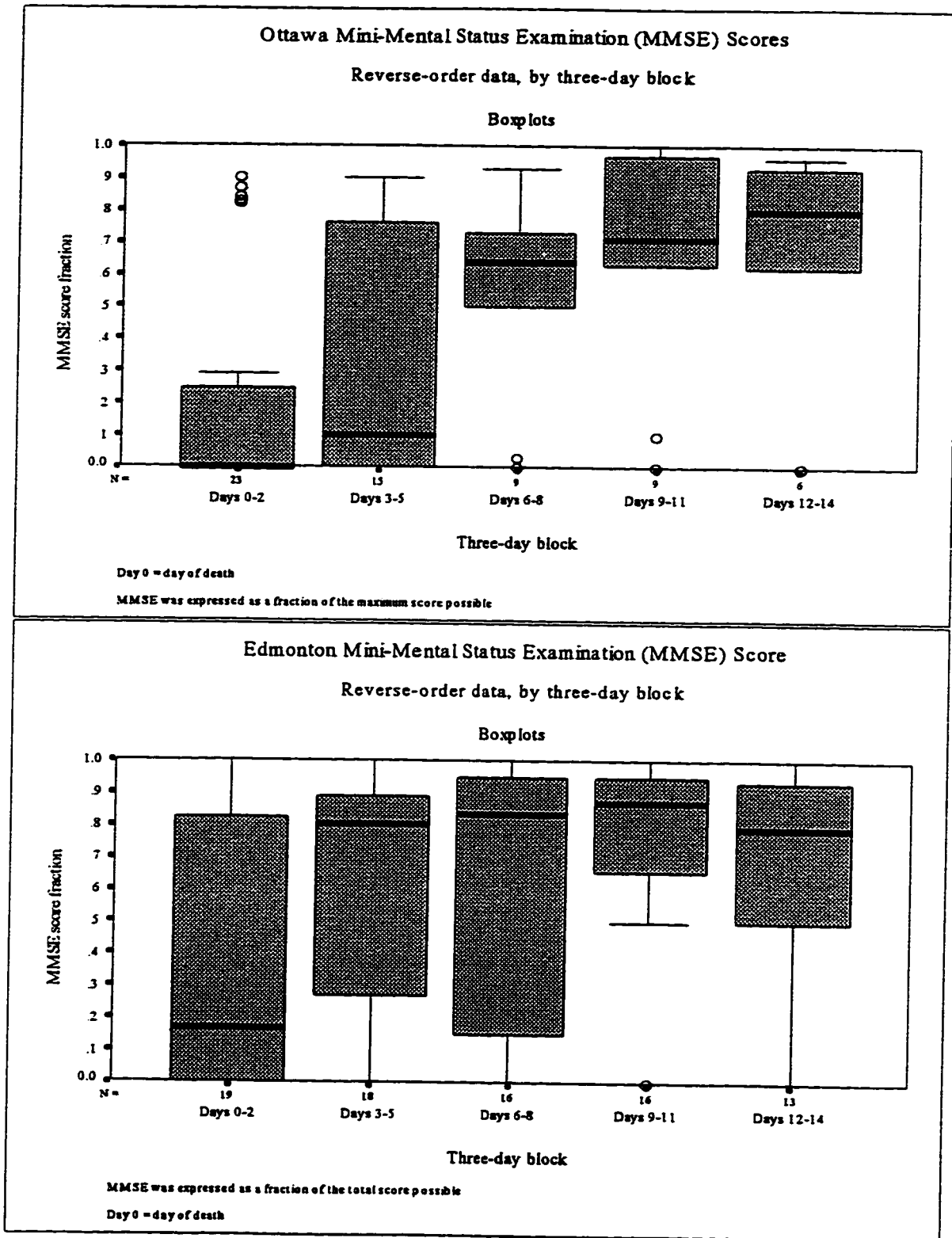


Figure B.29 Delirium Rating Scale Score

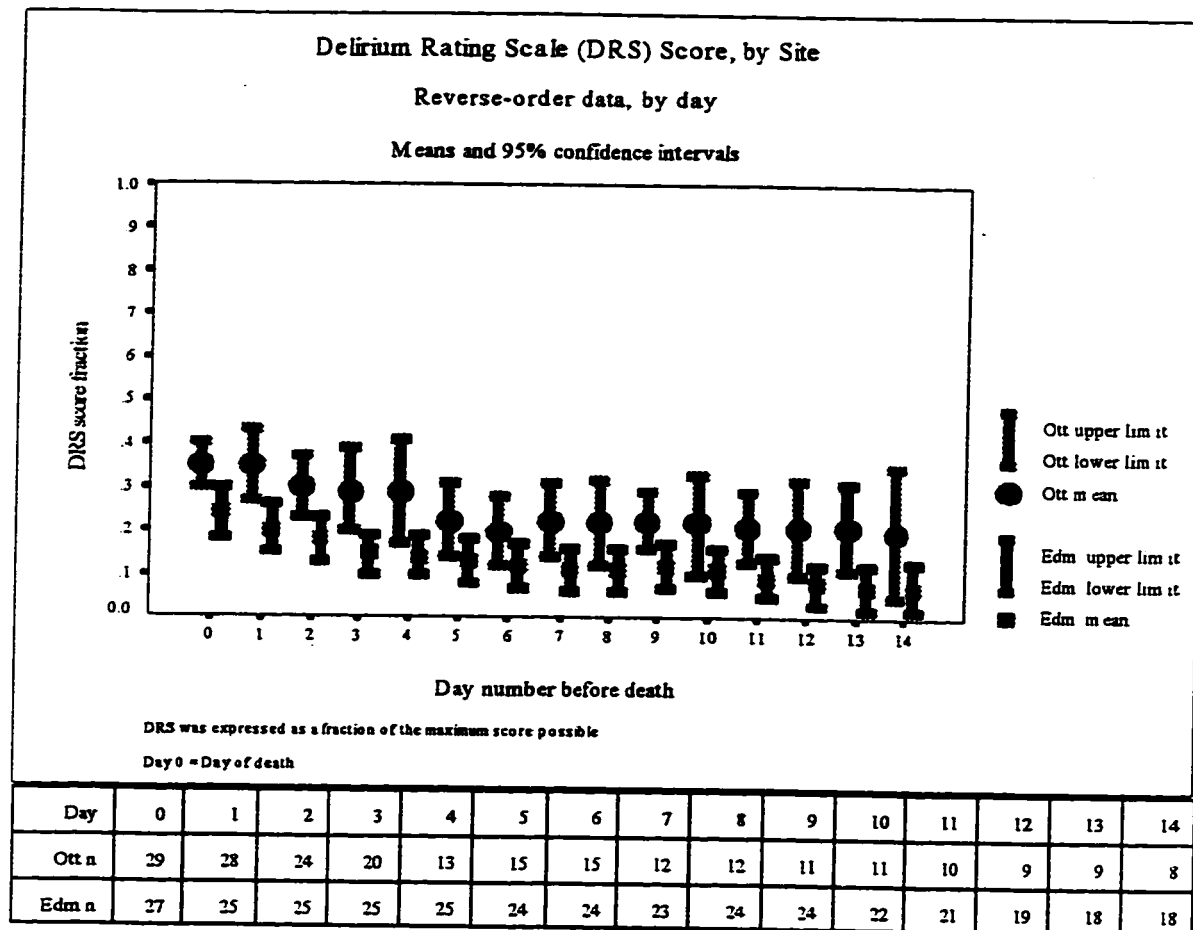


Figure B.30 Delirium Rating Scale Score

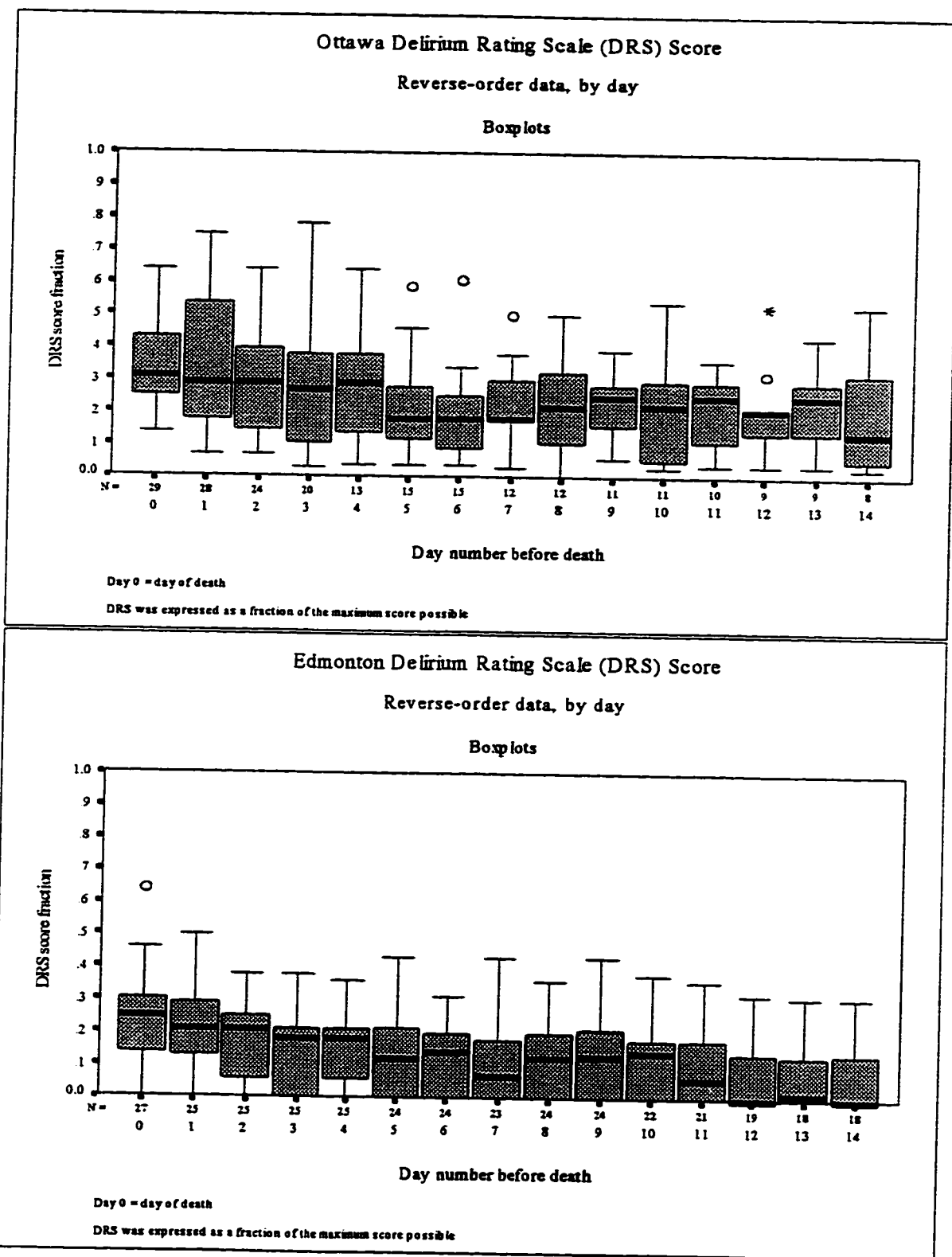


Figure B.31 Percentage of Visual Analogue Scales Completed by Staff

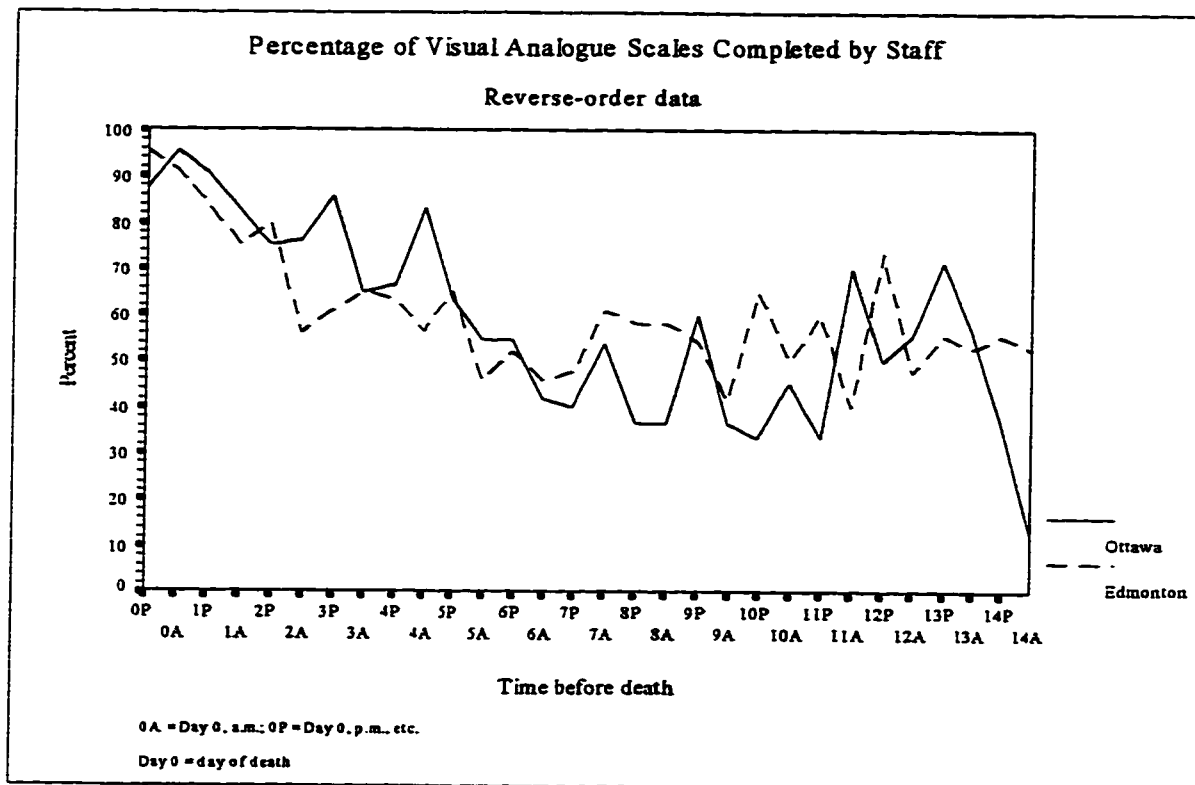


Table B.8
100 mm Visual Analogue Scale (VAS) Score for Ottawa
Reverse-Order Data for Days 0, 7 and 14
Means (SD)

VAS Item	Day 0		Day 7		Day 14	
	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Pain	11.7 (19.8) n=21	18.6 (17.5) n=7	29.6 (22.3) n=13	25.5 (25.4) n=10	24.4 (30.1) n=8	33.1 (29.1) n=8
Activity	95.7 (10.9) n=22	84.3 (17.9) n=7	72.7 (32.3) n=13	76.5 (31.9) n=10	75.6 (24.1) n=8	55.6 (36.5) n=8
Nausea	6.8 (21.4) n=22	2.9 (3.9) n=7	7.5 (14.4) n=12	35.5 (40.5) n=10	18.8 (30.0) n=8	20.6 (29.0) n=8
Depression	23.8 (30.9) n=4	10.0 (13.2) n=3	34.4 (35.4) n=9	41.9 (33.8) n=8	31.3 (34.7) n=8	21.4 (29.5) n=7
Anxiety	25.0 (29.7) n=6	13.3 (18.9) n=3	25.6 (34.3) n=9	38.8 (37.2) n=8	28.8 (22.5) n=8	28.6 (31.5) n=7
Drowsiness	80.5 (25.2) n=21	70.8 (32.9) n=6	64.6 (26.7) n=13	72.0 (34.3) n=10	56.3 (31.1) n=8	65.0 (24.5) n=8
Appetite	93.9 (20.2) n=22	98.6 (2.4) n=7	73.1 (34.3) n=13	93.0 (10.3) n=10	53.8 (39.1) n=8	71.3 (32.7) n=8
Wellbeing	76.3 (29.5) n=4	80.0 (14.1) n=2	59.4 (30.5) n=8	52.9 (28.7) n=7	58.1 (21.2) n=8	63.3 (29.9) n=6
Dyspnea	34.0 (37.4) n=21	30.8 (32.8) n=6	24.1 (27.7) n=11	35.5 (44.2) n=10	25.0 (31.8) n=8	22.5 (30.7) n=8
Weakness	95.2 (10.4) n=21	90.0 (12.2) n=6	80.8 (21.0) n=13	76.1 (28.0) n=9	61.3 (30.2) n=8	57.1 (29.7) n=7
Thirst	36.4 (30.5) n=21	14.2 (20.8) n=6	58.3 (36.7) n=12	45.0 (36.5) n=9	56.3 (24.0) n=8	56.4 (37.4) n=7
Dry Mouth	63.9 (32.2) n=22	41.7 (39.8) n=6	65.8 (31.4) n=13	52.2 (32.3) n=9	56.9 (27.2) n=8	51.4 (29.8) n=7

Table B.9
100 mm Visual Analogue Scale (VAS) Score for Edmonton
Reverse-Order Data for Days 0, 7 and 14
Means (SD)

VAS Item	Day 0		Day 7		Day 14	
	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Pain	18.3 (21.7) n=24	23.2 (23.0) n=23	22.9 (22.0) n=23	24.1 (18.4) n=24	31.6 (27.1) n=19	27.3 (25.4) n=18
Activity	89.5 (16.5) n=24	90.4 (18.2) n=23	78.3 (25.3) n=23	77.5 (26.5) n=24	80.2 (18.8) n=19	78.7 (18.6) n=18
Nausea	9.8 (13.2) n=24	16.0 (26.9) n=23	16.3 (19.6) n=23	17.4 (22.4) n=24	20.4 (23.3) n=18	23.2 (29.9) n=17
Depression	19.6 (26.4) n=21	29.4 (26.3) n=19	33.7 (25.5) n=21	31.3 (26.5) n=23	23.0 (23.1) n=18	27.9 (31.7) n=16
Anxiety	20.0 (23.6) n=22	23.1 (28.4) n=21	31.7 (27.7) n=23	29.3 (28.5) n=23	36.1 (29.0) n=19	38.6 (25.1) n=17
Drowsiness	73.3 (27.1) n=24	80.0 (26.3) n=23	65.7 (28.3) n=23	60.0 (29.8) n=24	62.7 (30.2) n=18	56.3 (32.8) n=18
Appetite	93.7 (9.4) n=24	89.6 (16.3) n=22	80.9 (21.8) n=23	74.3 (23.7) n=24	68.7 (25.1) n=18	76.3 (27.2) n=18
Wellbeing	62.1 (36.3) n=19	69.3 (31.9) n=18	56.6 (29.9) n=23	61.6 (24.9) n=24	51.9 (23.1) n=16	50.3 (30.1) n=17
Dyspnea	40.0 (33.0) n=24	42.0 (29.7) n=23	29.7 (27.5) n=23	33.8 (25.2) n=24	35.9 (29.0) n=18	34.9 (28.1) n=18
Weakness	82.2 (24.6) n=19	82.1 (31.7) n=17	75.8 (22.3) n=19	66.3 (23.1) n=19	65.5 (28.2) n=15	74.8 (21.2) n=14
Thirst	24.4 (28.9) n=18	27.8 (34.3) n=16	35.8 (30.6) n=19	51.7 (29.3) n=19	36.3 (32.1) n=15	32.5 (27.9) n=14
Dry Mouth	66.7 (33.2) n=19	55.6 (40.1) n=17	54.7 (27.8) n=19	64.8 (27.8) n=19	51.4 (34.3) n=15	45.3 (35.7) n=14

Figure B.32 24-hour Oral Morphine-Equivalent Dose

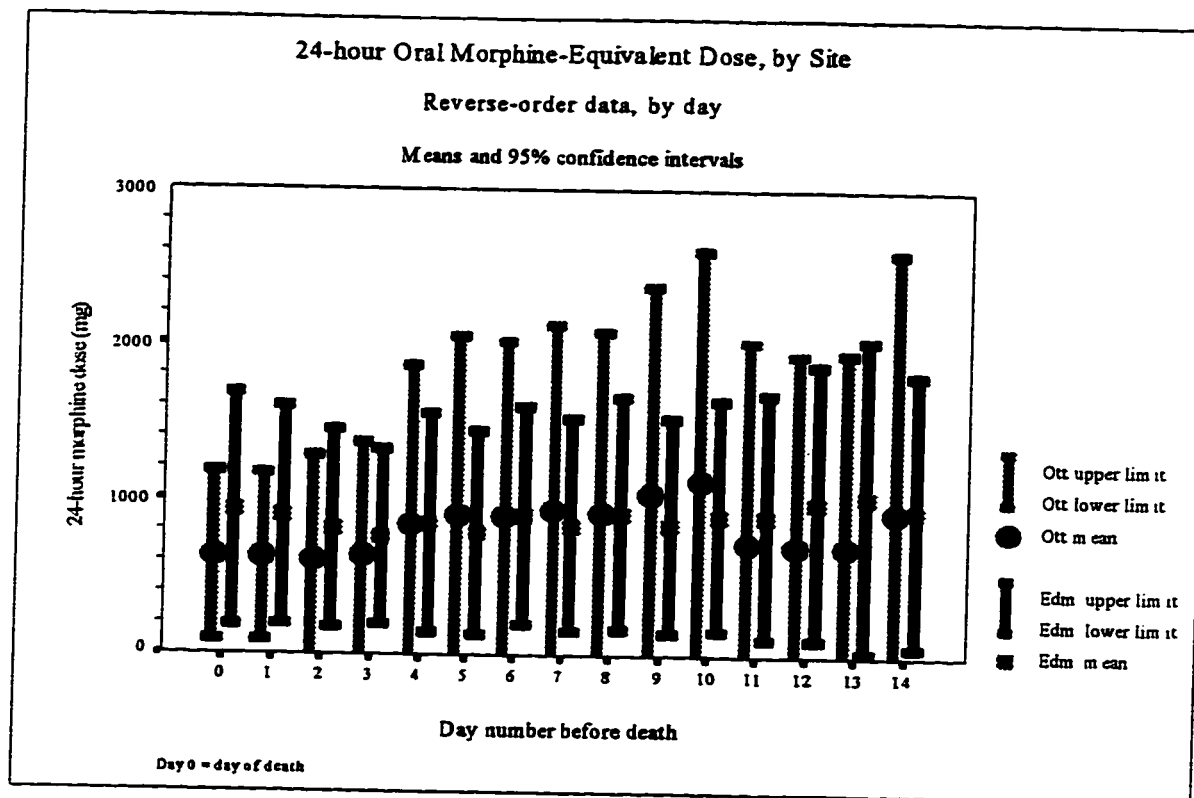


Figure B.33 24-hour Oral Morphine-Equivalent Dose

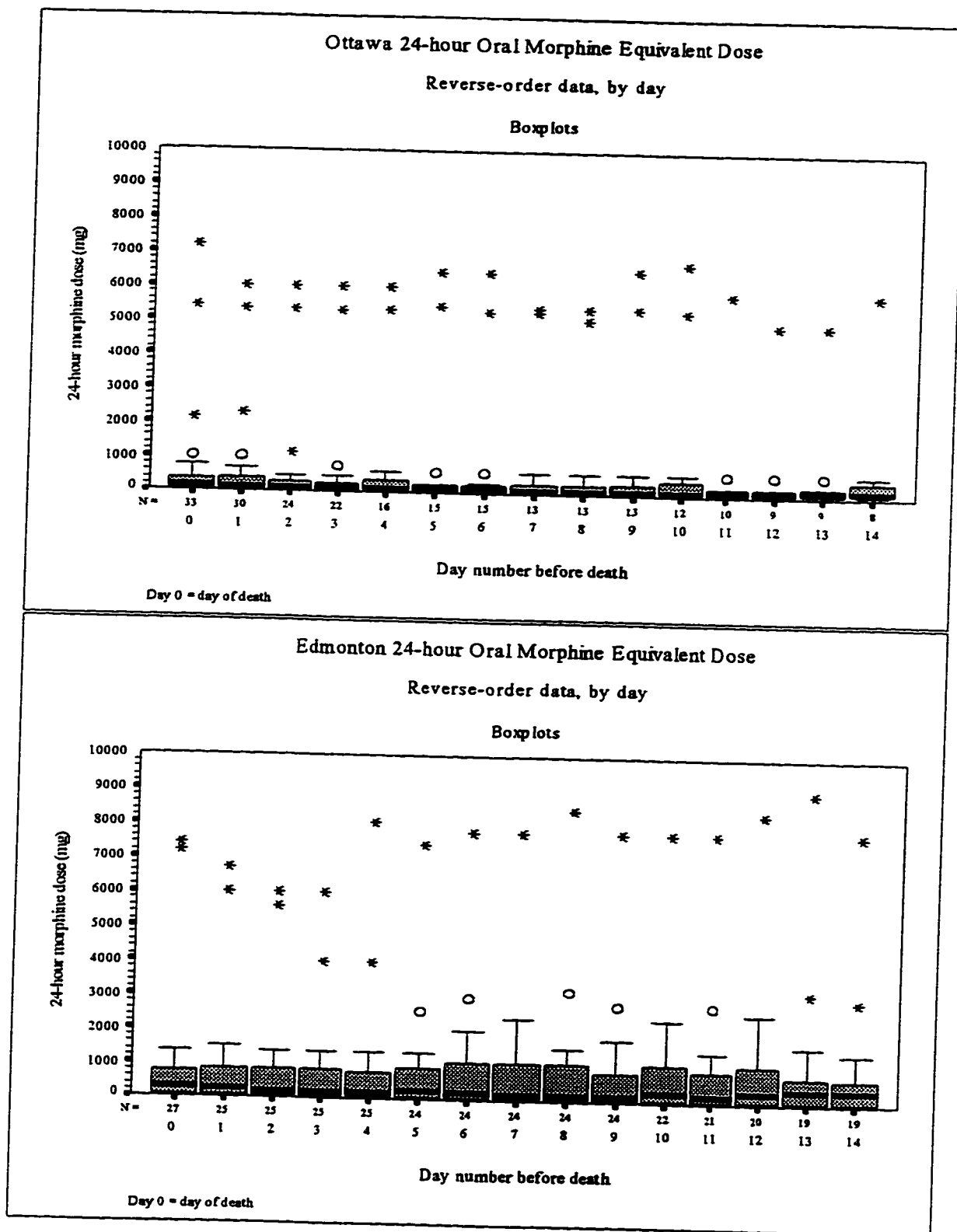


Figure B.34 Sedating Agent Use

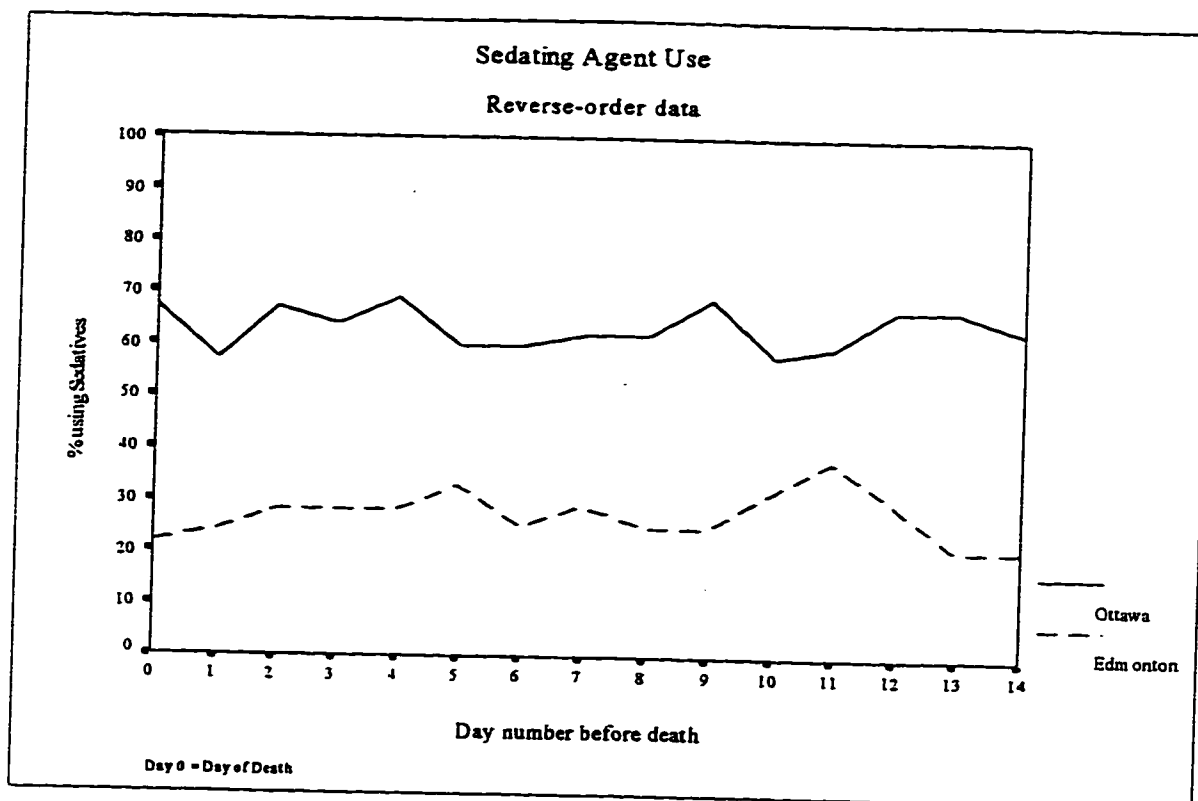
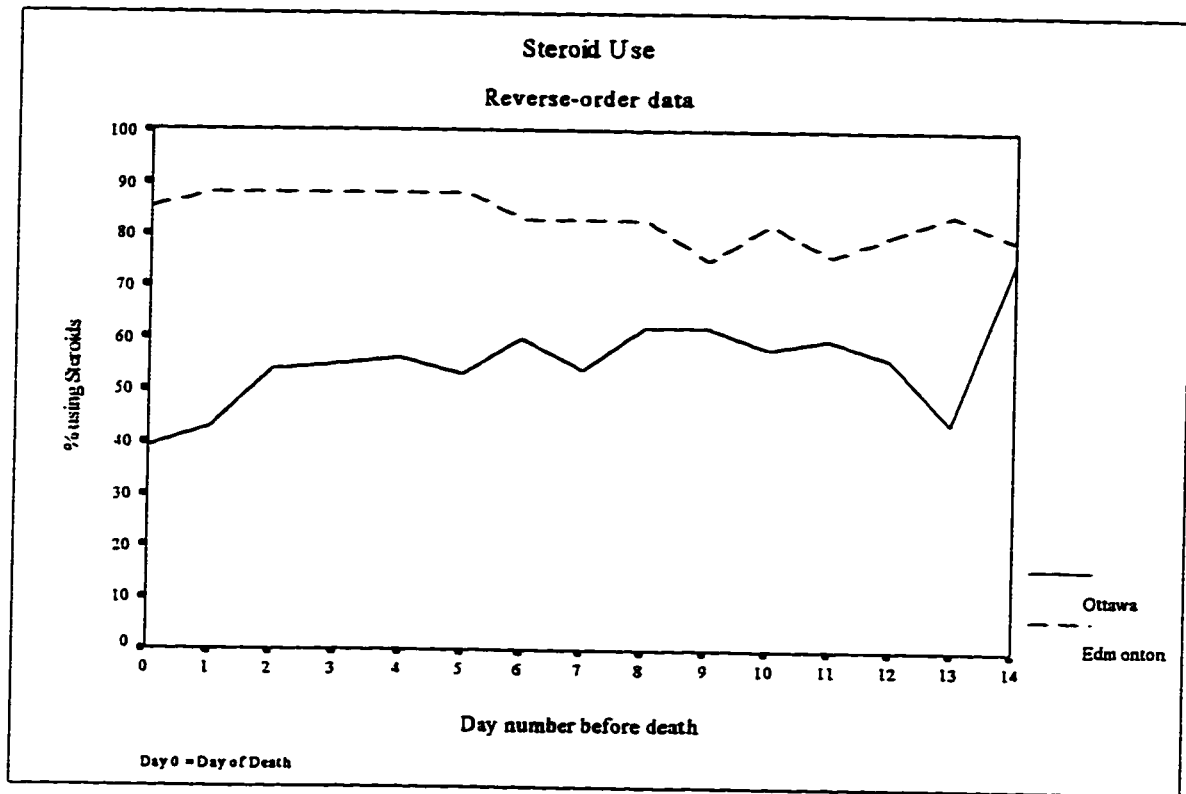


Figure B.35 Steroid Use



APPENDIX C

JOURNAL SURVEY TABLES

Table C.1
Information on the Journals Selected for the Survey

Journal Name	Information
Journal of Palliative Care (JPC)	- published since September, 1985 - included in Index Medicus since 1988 - 4 issues per year - published in Canada
Palliative Medicine (PM)	- published since January, 1987 - included in Index Medicus since 1993 - 4 issues per year - published in the United Kingdom
Journal of Pain and Symptom Management (JPSM)	- published since January, 1986 - included in Index Medicus since 1993 - 8 issues per year (12 starting 1996) - published in the United States

Table C.2
Primary Research Purposes
- Categories and Definitions

Category	Definition
Therapy study	evaluates benefits and/or risks of one or more interventions provided to patients
Diagnostic test evaluation	evaluates the performance of one or more processes for diagnosing a disease or condition
Risk factor study	identifies patient characteristics which may predict the likelihood of developing a disease or condition
Prognostic study	identifies patient characteristics which may predict the likelihood of one or more outcomes of a disease or condition
Clinimetric study	develops and/or evaluates an instrument to describe or measure a clinical phenomenon
Incidence-prevalence study	estimates the prevalence and/or incidence of one or a small number of diseases/conditions in a population
Needs assessment	identifies a population's multiple care needs for which health care services can be planned
Assessment of knowledge, attitudes and behaviour	assesses one or more of these aspects of a population with respect to specified conditions, diseases or services
Satisfaction with care assessment	assesses the degree of satisfaction in a population with respect to health services provided (a narrow form of program evaluation)
Program evaluation	assesses the impact of one or more health services, but not only nor primarily with respect to satisfaction with care
Patient profile assessment	describes multiple characteristics of a population (may help with service planning, but needs assesement not the primary aim)

Table C.3
Number of Eligible Articles Labelled With Each
Design and Purpose in the Three-Journal Survey

Purpose												
Design	therapy	diag test	risk factor	prognost	clinimet	incid-prev	needs	kab	satisfac	program evaluat	patient profile	total
experimental												
randomized, comparative	2											2
randomized, crossover	4											4
non-randomized, comparative	1											1
time series	13											13
non-experimental												
multiple cohort, retrospective							1					1
single cohort, prospective	1	1		2	2	3	1		1			11
single cohort, retrospective	3			2			3			5	3	16
cross-sectional		1	1		3	1	1	2	4	1	4	18
case-control			1									1
other												
other	1								1			2
total	25	2	2	4	5	4	6	2	6	6	7	69

diag test = diagnostic test evaluation; prognost = prognostic study; clinimet = clinimetric study; incid-prev = incidence-prevalence study; needs = needs assessment; kab = assessment of knowledge, attitudes and behaviour; satisfac = satisfaction with care assessment; program evaluat = program evaluation

Table C.4
Designs and Purposes of 34 Studies Whose Articles Did Not
Indicate Facing Any Obstacles, Relative to the Total Sample
of 69 Studies in the Three-Journal Survey

Purpose												
Design	therapy	diag test	risk factor	prognost	clinimet	incid- prev	needs	kab	satisfac	program evaluat	patient profile	total
experimental												
randomized, comparative	0/2											0/2
randomized, crossover	1/4											1/4
non- randomized, comparative	1/1											1/1
time series	4/11											4/11
non- experimental												
multiple cohort, retrospective							1/1					1/1
single cohort, prospective	1/1	0/1		1/2	1/2	1/3	0/1		0/1			4/11
single cohort, retrospective	1/3			2/2			1/3			2/5	2/3	12/16
cross- sectional		1/1	0/1		1/3	0/1	0/1	2/2	1/4	1/1	1/4	9/18
case-control			1/1									1/1
other	1/1								0/1			1/2
total	11/25	1/2	1/2	3/4	2/5	1/4	4/6	2/2	1/6	3/6	5/7	34/69

diag test = diagnostic test evaluation; prognost = prognostic study; clinimet = clinimetric study; incid-prev = incidence-prevalence study; needs = needs assessment; kab = assessment of knowledge, attitudes and behaviour; satisfac = satisfaction with care assessment; program evaluat = program evaluation

APPENDIX D

**ARTICLES INCLUDED IN THE SURVEY OF THREE PALLIATIVE
CARE JOURNALS**

D.1 Journal of Palliative Care

- 1 Pannuti F, Tanneberger S. The Bologna Eubiosia Project: hospital-at-home care for advanced cancer patients. 1992;8(2):11-17.
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APPENDIX E

OBSTACLES IDENTIFIED IN THREE-JOURNAL SURVEY

OBSTACLES IDENTIFIED IN THREE-JOURNAL SURVEY

The obstacles identified are discussed under the four main theme headings, which are:

- (1) Patients' Conditions;
- (2) Ethical Concerns Regarding the Patient and Informal Carers;
- (3) Population Heterogeneity; and
- (4) Lack of Relevant Outcome Measures

Patients' Conditions

The poor and usually unstable conditions of palliative care patients was an obstacle to research which had several different effects in studies, and sometimes multiple effects in the same study. It affected: recruitment to studies; the informed consent process; the patient's ability to receive the intervention; the patient's ability to be a source of information; the quality of data collected from the patient; the consistency of data collection, resulting in missing data; and the patient's ability to remain in the study, potentially resulting in censored data.

Effect on Recruitment to Studies

In four studies the authors recorded experiencing recruitment limitations because some patients' conditions affected their ability to take part. In three other studies with recruitment difficulties the causes were less clear. Bruera et al. had relatively minor problems when, out of 61 consecutive patients, four (7%) were excluded because "severe cognitive failure" made the assesement of symptoms impossible¹. Burge's study², included in the systematic review in Chapter 2 and eligible for this survey as well, experienced severe accrual limitations because of eligibility criteria which included the "ability to understand, give consent, and participate in the study...". Because of this,

out of 123 patients considered for the study, 20 were excluded for confusion, 17 because of being too weak to participate, 13 for drowsiness or coma, 2 for aphasia, and 2 for anxiety or agitation. Another five patients died before they could take part. (In contrast to the recruitment-exclusion numbers, only five other patients declined participation.) Two palliative care units were used to access patients, which may have helped to partially offset the recruitment problem with respect to sample size, but the author acknowledged that the exclusions limited the generalizability of the results. In a study by Power et al., out of 100 patients eligible to be entered into a study upon admission to a terminal care unit, two refused and seven died before the first assessment 24 hours later³. In the fourth study, by Higginson and McCarthy, 183 patients were available for the study upon referral to two community support teams in the United Kingdom⁴. The protocol called for the first research contact two to four weeks later, at which time 69 had died and 14 were too ill to participate, leaving only 55% of the original sample to approach for participation. (Another 16 patients did not take part in this study because of refusal by the patient, the carer or the general practitioner.) The authors noted that similar low response rates had been encountered by others doing research with the dying and acknowledged that selection bias may affect such studies.

Among the three studies with no clear cause for recruitment problems, Deschamps et al. stated that "...the disease is often advanced and the physical condition may deteriorate rapidly...patients who were eligible for a study may no longer fulfill the eligibility criteria when treatment is scheduled to begin, or those who enter the trial may become too ill to complete it"⁵. This paper reported a randomized, crossover, analgesic study involving four cancer centres, yet only enrolled 20 patients initially. No explanation was given for this initial sample size. The eligibility criteria may

have limited recruitment, since they restricted eligibility to patients who had normal hematologic, hepatic and renal function and who were mentally and physically able to take part in the study. In addition, they excluded those who were undergoing active anti-cancer treatments, were receiving other pain therapies or were unable to take oral medications. Excluded patients were not enumerated or described. The study involved a titration phase of up to 10 days prior to the trial phases, and six of the 20 patients (30%) did not complete the titration phase (one died, four developed other severe symptoms, and one withdrew consent).

A sixth study, by Forman et al., reported "slow accrual" to a 30 day, multicentre, time series, analgesic trial. The trial was closed early because of this⁶. No explanation for the accrual problem was given, but one of the criteria for excluding a patient was that patient was "not expected to survive for the duration of the trials". Recruitment exclusions were not enumerated or described, so the nature of the obstacles to recruitment were unknown. Similarly, in an analgesic trial by Boureau et al., which used a randomized, crossover design⁷, the investigators' goal was to enroll 60 subjects from six centres. They experienced "recruitment problems", which were not described, and eventually recruited 52 subjects from nine centres over 21 months. Amongst other exclusion criteria, they excluded patients who were unable to respond to questions asked, who had difficulty with swallowing or who demonstrated progression of the underlying disease suggesting deterioration. Recruitment exclusions were also not described.

Effect on the Informed Consent Process

Bruera et al., in a prospective, single cohort study, found that the incidence of cognitive failure was so high in the group of palliative care unit inpatients studied (66 episodes in 47 patients) that they stated:

Our findings suggest that communication between the patient and the family and medical staff during the last week of life is usually difficult. As a result, informed consent for therapeutic or research procedures or resuscitation guidelines may be impossible to obtain reliably during this period.⁸

Irrespective, then, of whether the patient could take part in the study protocol, the ability of the patient to give informed consent for participation was identified as a factor affected by the patient's condition. Burge, cited above, excluded patients who were unable to understand and consent to participation in his study, in addition to considering their ability to take part.

The effect of cognitive status and competence on the consent process was not otherwise specifically cited as an obstacle in any of the studies surveyed, but two studies raised questions related to this issue. Walker's study⁹ required written, informed consent from each patient, but also obtained written consent from the patient's consultant and home care sister and verbal permission from the patient's general practitioner to allow the patient to take part in her study. There was no indication that the family or designated substitute decision maker was involved in the consent process. The study used a time series design to assess the effect of an information leaflet on 15 study patients' pain control knowledge, using pre- and post-leaflet interviews one week apart and a home pain diary to measure the impact. The author stated in the results section that some patients (the exact number was not given) "were too ill and experiencing too much pain to be able to use the leaflet effectively", then discussed the "limitations of giving written information". In the study by Power et al., a cross-sectional design was used to assess the prevalence of cognitive impairment and depression in a group of patients consecutively admitted to a terminal care unit. Verbal consent was obtained from the patients and only two out of 109 patients refused to take

part. Cognitive testing occurred within 24 hours of admission and 30 out of the 87 reported patients scored low enough to be deemed to have 'significant cognitive impairment' (prevalence of 34%). Eighty-one of the 87 also took part in a brief depression screening interview, six others being too confused to respond to questions adequately. These two studies demonstrated the potential for obstacles to informed consent to be present even if the investigators were unaware of them.

Effect on the Patient's Ability to Receive the Intervention

Three studies commented on the effect the patients' conditions could have on their ability to receive the intervention. As mentioned previously, Walker noted that some of the patients in her study were unable to use the pain leaflet effectively because of their illness and level of pain. Walsh et al. reported a time series trial of patient-controlled analgesia (PCA) involving nine patients¹⁰. Two patients (22%) had to have their PCA stopped because their mental status deteriorated (one died shortly after while the other recovered and restarted PCA). Yajnik et al. studied the use of phenytoin as a coanalgesic in a randomized, comparative trial, but reported using relatively modest doses of the study drug, at least partly because of the poor condition of the patients involved¹¹.

Effect on the Patient's Ability to be a Source of Information

Eleven studies noted or dealt with methodological difficulties associated with the use of terminally ill patients as sources of information. Sykes et al. decided to conduct their study of satisfaction with care by interviewing carers of patients dying of cancer six months after the death had occurred, with part of the justification for this approach being to avoid the "clear methodological...difficulties raised by using the patient to gain information"¹². They did not elaborate on the difficulties which concerned them. Boyd

reported a retrospective study to evaluate the care of patients admitted to an inpatient hospice for the last 48 hours of life¹³. In addition to other concerns, they found that many patients were too ill to answer detailed questions or to do symptom scoring; instead, the staff performed the assessments and a retrospective design was used. Krech et al., in a cross-sectional survey to describe symptoms in patients with lung cancer noted that the group with the worst performance status reported the lowest median number of symptoms¹⁴. In their discussion they felt that this was unlikely to be due to a true decrease in symptoms, but probably was the result of "the difficulty of interviewing patients secondary to the severity of the disease". They pointed out that of the 12 patients in the poorest performance status group, four were dyspneic, four were confused, three were both dyspneic and confused, and one was hypercalcemic. They go on to state that "being too ill to communicate a symptom does not indicate its absence". The poor condition of palliative care patients was believed to be an obstacle to the collection of complete data directly from patients.

In another cross-sectional survey, the planning of the study took into consideration the patients' conditions and their ability to provide information¹⁵. The adjustments made were the following: a questionnaire was administered to the patients as a structured interview, rather than in writing, due to the patients' poor health; the scope of the study was limited partly for the same reason (it did not incorporate a test-retest evaluation of the interview instrument); and patients were included only if they were "well enough to be interviewed" (the number excluded for this reason was not given). Much of the concern here seemed to be with the patients' physical ability.

There were other examples of studies which used strategies to deal with expected limitations in patients' ability to provide outcome information. One was illustrated

in the study by Boys et al. in which visual analogue scales (VAS) were used to assess pain in a time series study auditing the use of neural blockade in 125 patients¹⁶. Patients who were unable to complete the VAS were asked to score their pain on a verbal scale from 0 to 10 instead. Neither the reasons for patients not being able to complete the VAS nor the proportion of patients who used the alternate method were given, although all of the subjects were able to do one or the other. Bruera et al.⁸, in their study cited earlier, wanted to assess the cognitive status of patients three times per week, from admission to a palliative care unit until death or discharge. These patients were described as "extremely debilitated", but despite this the investigators felt that they were able to successfully use a cognitive screening instrument, the Mini-Mental State Examination¹⁷. They reported that this was simple and could be repeatedly used with these very ill patients. Power et al., in their study to screen for cognitive impairment and depression, were concerned that lengthy or self-administered questionnaires were poorly tolerated by patients. They used brief instruments which did not require self-administration, an Abbreviated Mental Test Score (AMTS) and a semistructured depression assessment, the latter adapted from an existing instrument. Eighty-seven patients were reported. All were assessed with the AMTS, but six were too confused to be able to do the depression interview. The authors felt that both instruments were well tolerated. Dudgeon et al. performed a study to determine correlation coefficients between long and short versions of the McGill Pain Questionnaire in advanced cancer patients¹⁸. Such studies had been done previously in other patient groups. Because the short version took less time to complete and was easier to understand than the longer form, they felt that the former would be an alternative multidimensional pain assessment tool for use in studies involving patients with advanced cancer "who have difficulty concentrating for

prolonged periods of time". Higginson et al., mentioned earlier, wanted to test the validity of their instrument, the Support Team Assessment Schedule (STAS), by comparing ratings made by patients, carers and staff. The tool consisted of 17 items, but they decided to limit this study to seven items, partly due to the poor condition of the patients. Ratings were provided by patients and their carers through independent interviews; however, as reported earlier, some patients were too ill to participate despite the shortened questionnaire.

The possibility of using a surrogate to provide outcome information on behalf of patients did not arise in very many studies at all. Corli et al. tested an instrument for measuring food quantification in a group of 75 palliative care patients whose life expectancy was more than two months¹⁹. The patient completed the instrument daily until death, with a family member taking on this task if the patient lost the ability. The authors did not provide the number of patients who required reporting by a surrogate. On the other hand, Burge specifically excluded from his cross-sectional study all patients who could not complete his seven item visual analogue instrument themselves.

Effect on the Quality of Data Collected from the Patient

Krech et al. found it difficult to interview patients with severe disease and wondered about the completeness of the data obtained. The overall quality of data obtained in palliative care studies was another issue raised by three other studies. In Walker's study evaluating the effect of a pain control leaflet, discussed previously, all patients completed a pain diary and were assessed by semistructured interviews. The author did not comment on the perceived quality of the data provided by the patients through these methods, even though, as mentioned earlier, she reported that some of the 15 patients had trouble using the leaflet effectively because they were too ill or in too much pain.

Ernst et al. conducted a randomized crossover study evaluating a therapy for bone pain²⁰, and used the patient's and the investigator's preferred choice of therapy as one of the outcome assessments. Out of 21 patients, 12 chose the study medication, 4 chose the placebo and 5 had no preference. The investigator, who had access to the VAS scores and analgesic profiles, chose the study drug 14 times and the placebo six times and had no choice only once. Noting that the investigator made a choice more frequently, the authors felt that the patients' fatigue and cognitive impairment, related to advanced cancer and the use of medications, may have contributed to some patients lacking the ability to notice a difference between therapies. They used this finding to support the practice of using a number of different methods to evaluate response in an intervention trial.

The planning of this same study incorporated methods to try to optimize the quality of other outcome measures, which included a daily analgesic log and multiple daily VASs completed by the patients. The patients were instructed on the proper method of doing the VASs and, as well, weekly supervision of the patients with respect to completion of these instruments was included in the study. The authors felt closer follow-up might have produced even more accurate data, citing other studies that utilized daily coaching of patients regarding the use of VASs; however, they did not present any evidence that the VAS data obtained suffered in quality with the study as it was.

Walsh et al.'s time series of PCA analgesia included, out of the nine patients in the study, one patient (11%) who appeared to be unable to understand the use of visual analogue scales and could not produce "meaningful data". Whether or not this was due to the patient's poor condition related to terminal illness was not made clear in the article.

Effect on the Consistency of Data Collection

In five studies the problem of missing data was raised. Ernst et al., discussed above, were successful in having all VASs completed by 95% of the 21 patients who finished the study (three patients did not finish). This may have been at least partially due to their methods of optimizing data collection. Walsh et al. reported that three of nine patients (33%) in their study had insufficient VAS data to allow for assessment of outcomes. They did not give any reasons for these missing data. In the same study, only five out of nine patients had enough investigator-assessed data on alertness to be interpretable, but again, this was not explained. In Forman et al.'s study, cited earlier, out of 69 patients entered 16 were removed from the trial for various reasons. Not all of these reasons were specific for the palliative care setting, but six of these patients were removed because they had missing data. The reasons for the missing data were not given.

In a prospective, single cohort study by Peruselli et al. 40 patients receiving home care for at least one week were to complete a weekly self-report of their symptoms until the end of their home care program²¹. Only 15 (38%) successfully accomplished this in a complete and consistent way. In the case of 23 others, the authors stated that the "assessment was incomplete due to worsening of the patient's clinical condition, enabling only partial completion of the record". Two other patients refused to complete the reports. Patients with incomplete data were totally excluded from the analysis that required the patient self-report data. In Higginson et al.'s study introduced earlier, some questions in the interviews of patients or carers were missed, for reasons that included respondent fatigue in addition to question irrelevance and the respondent's inability to assess an item. More missing items occurred with patient interviews than with carer interviews. The analysis excluded the missing items.

Effect on the Patient's Ability to Remain in the Study

Fourteen studies dealt with a significant number of patients who were lost to the study after it had started, often resulting in a lack of most if not all outcome assessments for those patients. A randomized, controlled trial of an oral spray for mouth symptoms planned to recruit hospice inpatients for a two week study, with assessments at baseline, one week and two weeks²². Anticipating losses to follow-up, the investigators apparently inflated the recruitment goal and recruited 197 patients who were admitted consecutively to their hospice. No sample size justification or pre hoc estimation of losses were given. There were no reported exclusions or refusals at recruitment, but by the one week assessment point 101 (51%) had died and by two weeks 153 (78%) had died. An even number of patients remained in each group at each follow-up point. Analysis was carried out on changes in the assessments from baseline to each of the two follow-up points. Patients who survived to the one week point contributed to that analysis, but were removed from the two week analysis if they died before that point. The results were all negative, but no power calculation was made nor were confidence intervals given, although the latter could be calculated for some variables. The effects of the censoring on internal and external validity were not addressed. The authors stated that there were no means of increasing the proportion of patients who completed such a study unless patients at an earlier point in the disease process were enrolled.

In Corli et al.'s study to test their instrument for measuring food quantification in 75 patients, the investigators wanted to analyze data from the first two weeks of home care and then from the last four weeks of life. Because of this, they decided to exclude from the analysis any patients who died less than six weeks after starting the study. They did not give the number of patients excluded for

this reason.

Crossover studies pose a particular dilemma when subjects are lost to followup. In Ernst et al.'s crossover trial, discussed previously, three patients out of the 24 initially recruited (13%) were unable to complete the 14 day study, one because of a possible side effect of the study therapy, and two because of the development of cognitive failure. All three were excluded from the analysis. In another crossover trial by Bruera et al.²³, one of the eleven patients enrolled (9%) developed an intercurrent illness 24 hours after entering the study and had to be removed from the analysis as well.

Complete exclusion from the analysis of patients who are unable to complete a study occurred in non-crossover designs as well. Peruselli et al. conducted a prospective, single cohort study of 40 terminally ill home care patients to assess nursing diagnoses and their degree of agreement with patients' reports. Twenty other patients were excluded because they had received home care for less than one week, considered too short of a period of observation for this study. It was not stated what happened to these patients to cause their exclusion on this basis. In a small time series trial lasting four weeks²⁴, only seven patients out of the original ten completed the study and were able to do both of the scheduled follow-up assessments at two and four weeks. One patient died at two weeks and two developed intercurrent illnesses and were removed. Dudgeon et al.'s prospective, single cohort study to correlate the short and long versions of the McGill Pain Questionnaire entered 28 patients and involved administration of the two questionnaires on three occasions, each three to four weeks apart. Four patients (14%) died before completing the study and were completely excluded from the analysis (the timing of the deaths were not given). The scheduled assessments were all completed by the other 24 subjects. In another time series trial, Bruera et al.²⁵ entered 24 subjects, but two (8%) were not evaluable because one died

three days into the study and another withdrew consent to participate after four days. The study assessed the local tolerance to subcutaneous infusions of opioids and required involvement of at least seven days. Walsh et al.'s study, mentioned earlier, tried to follow nine patients with subcutaneous infusions of morphine for up to 30 days, but three (33%) died in less than one month (two of these deaths occurred after only four and six days). A descriptive analysis was presented.

The study by Walker et al., discussed earlier, to assess the pain control leaflet, scheduled two interviews with patients one week apart and enrolled 15 subjects. Four patients (27%) died before the follow-up interview. Information from these patients' first interview was provided. In Boys et al.'s time series trial of neural blockade, 25 of the 125 recruited subjects (20%) died before the two to six week follow-up assessment and were excluded from the data at that assessment only. Prior assessments were done pre-block and at 24 hours, with no patients dying before the 24 hour assessment. All other patients returned for the final assessment. Slover et al. performed a time series analgesic study with five patients²⁶, planning follow-up assessments at 15 and 30 days, but one patient died at two weeks and another on the final day of the study. All patients appeared to have been assessed and included in the data at two weeks, while only the three surviving subjects contributed to the data at the final assessment. In another small, time series analgesic trial Herbst et al. entered 11 subjects for a four week trial²⁷ with assessments at two and four weeks. The authors acknowledged the known short prognosis of their patient population, stating that the average length of care in their home-based hospice was 45 days. Before the end of the trial three patients had died and one was removed because of an intercurrent illness. The analysis included all 11 at week two, but only the surviving seven patients at week four.

In the study by Forman et al., as mentioned earlier, 16 out of 69 patients were removed from their time series evaluation of an opioid analgesic. The six with missing data were mentioned previously. Two others withdrew because they experienced nausea and vomiting, another withdrew because of progressive pain, and one died. The others were excluded because four could not be adequately titrated with morphine, one was found to be ineligible, and another developed a flare up of psoriasis. Only the 53 remaining (77%) were analyzed.

Ethical Concerns Regarding the Patient and Informal Carers Patients and Carers as Sources of Information

Several studies expressed ethical concerns and some made adjustments to their methodologies because of these concerns. Pannuti et al., in concluding their paper, suggested that a home care service should "monitor and assess the impact of the program on the patient's survival and quality of life, considering the technical and ethical points bearing on the same issue..."²⁸, suggesting that there are important ethical issues involved in assessing patient outcomes. They did not elaborate. Sykes et al. thought that there were not only methodological difficulties associated with using patients to acquire information for research (this concern of theirs was discussed earlier), but ethical ones as well; they did not elaborate on specific issues. Their study of satisfaction with care avoided these difficulties by using carers as the source of information and they noted that many studies of satisfaction with palliative care services have done likewise. In Boyd's retrospective study of short, terminal admissions to a hospice, there was concern that relatives and patients might be distressed by direct involvement in research, especially in view of the patient's admission and impending death. For this reason, and in addition to concern about the patients' ability to provide information mentioned previously, Boyd chose to use a retrospective design and to have the staff make the

assessments. In the discussion, the author stated that the concern around causing distress to the relatives was lessened by observing their positive response to the admission. Plans were expressed to obtain the relatives' views directly in a future study. Spiller et al., in comparing the views of terminally ill patients and their family caregivers shortly after admission to a palliative care unit, were concerned that this was a difficult time for patients and families. Partly because of this, they limited the scope of the study they otherwise would have liked to have done (they had considered including an evaluation of the test-retest reliability of the instrument used).

The Use of Investigative Technologies

The use of forms of investigative technology was a concern in two studies. Burge noted "ethical and comfort concerns of using accurate but invasive methodology" for the assesement of the fluid volume status of patients participating in research. He settled on using blood tests plus an estimate of fluid intake to assess fluid status. In a study to evaluate a clinical-severity assessment tool for terminally ill patients to help indicate appropriate transfers between health care settings, Strause et al. assessed only the first two parts of their instrument²⁹. Part three required a venipuncture to be performed on the patient, and the authors stated that this was "not routinely done in either a home care or outpatient setting". They did state later in the paper, without explanation, that an ongoing study included the third part. Eight other prospective or cross-sectional studies in this survey included venipunctures in their study protocols. In one, by Power et al., all patients scoring low on their cognitive screening tool were to have laboratory investigations performed, including blood tests. However, only 20 patients out of 30 had them done. The discrepancy was not explained. In contrast to that example, in Burge's study

51 out of 52 subjects had scheduled blood tests carried out.

Dealing with Sensitive Issues with Patients

Three studies were concerned about dealing with potentially sensitive issues when interviewing patients. Walker et al. decided to tape record the interviews so that the interviewer would not be preoccupied with writing. Power et al. felt that the need to ask about suicidal ideation and other sensitive issues as part of a screening instrument for depression was best handled discretely in an interview rather than by way of a self-administered questionnaire. A close relative usually attended the interview. Higginson et al., in testing the validity of seven of the 17 items in their STAS instrument, selected items partly on the basis of "ethical objections" to asking patients to assess certain items which may have been distressing.

Concerns About the Carer in Carer-based Studies

Ethical concerns regarding the carer were important in studies that focused on them as sources of information. In an interview-based study involving carers of dying patients admitted to an inpatient hospice³⁰, out of 104 carers, 17 were excluded because the investigators felt that it was inappropriate to ask for an interview if the patient was too ill or was very close to death. Only 11 declined to take part in the study. In Sykes et al.'s study, bereaved carers were interviewed about six months after the death. They chose to use a face-to-face interview rather than a questionnaire partly because of the ability of the specific interviewer to sensitively handle issues painful to the carer. In addition, the interview was thought to be potentially therapeutic for the bereaved. They were able to interview 106 out of 169 carers contacted (63%) and noted that previous response rates for such interviews, based on the experiences of others, increased if the interview was done nine months after the

death rather than at three months. Woodward's group arranged to hold focus groups for bereaved carers of deceased palliative care patients³¹. Their article reported on the first three groups. A total of twenty-five carers were randomly selected to attend. Twenty-one (84%) initially agreed, but then nine more decided not to go because "it was too difficult for them", leaving an overall attendance rate of 48%. Several of those who did attend found it difficult to do so. Based on this feedback, subsequent focus groups were delayed further from the time of death, to beyond six months instead of between four and six months after the death. The investigators planned to assess the possibility that selection bias existed, because of the pattern of response to these focus groups, by carrying out a postal questionnaire audit.

Wakefield et al. designed a study to interview surviving carers one year or more after the death of a family member, identified through a cancer registry³². They wished to include deaths that occurred in five different settings, so various research ethics boards were involved. This resulted in different approaches to the recruitment of subjects for the study, with most being sent a letter and receiving a follow-up phone call. For the cancer deaths that occurred at home, however, telephone contact to recruit carers was not allowed and the letter sent to this group included instructions to ignore it if participation was not desired. Anticipating a lower response rate from this group, the sample selected was doubled for this group only. The response rate from this group of potential subjects was only 37% compared to between 52% and 71% from the other four groups. One hundred carers were interviewed for the whole study.

Not all follow-up studies involving the bereaved had low response rates. Beck-Friis et al. sent questionnaires to 87 bereaved carers of terminally ill patients cared for by a hospital-based home care service³³. These were sent between six and 28 months after the death, and the study included a

reminder notice. The final response rate to this self-administered questionnaire was 94%. In Keizer et al.'s telephone survey of surviving carers of patients who had died in a palliative care unit³⁴, out of 60 randomly selected carers, 11 could not be contacted, two were ineligible, two declined saying they "did not wish to return to the past", and 45 were interviewed (96% of the eligible, contactable carers). The interviews occurred six to twelve months after the death.

Population Heterogeneity

Most authors did not comment directly on the heterogeneity of the palliative care population. Five articles made some reference to aspects of heterogeneity and its potential implications. Fainsinger et al. commented on the need to interpret cautiously the results of their study because of the different stages of cancer represented in the subjects at the time of study entry (in addition to the small number of subjects included)³⁵. Sykes et al. limited their study to the carers of persons who had died of cancer only, so that "the population under study could be defined accurately". They went further to define the sampling frame of terminally ill patients specifically with respect to age limits, residency and date of death. Burge excluded non-cancer patients and patients with a life expectancy of more than six weeks in his cross-sectional study to assess the association of fluid status measures with symptoms. He did not explain the restriction to cancer patients only, but the restriction with respect to prognosis was used to exclude patients who were earlier in their disease and not likely to experience the clinical condition of 'terminal dehydration'. Despite this, the study sample still included some patients who survived several months and the author wondered whether these patients may have had "a very different experience of thirst" compared to those who died soon after the study. He used multivariate as well as univariate analyses.

In a multicentre, randomized, crossover trial of clodronate for metastatic bone pain performed by Ernst et al., the 24 recruited patients showed evidence of heterogeneity in their baseline characteristics. Their ages ranged from 36 to 88, several different primary malignancies were represented, and the baseline oral morphine-equivalent dose varied from 6 mg to 640 mg per day. The investigators had restricted enrollment to patients who had not received any radiotherapy to a painful site nor had undergone changes to systemic hormonal therapy or chemotherapy in the previous four weeks. They reported that the exclusion of patients who had received recent radiotherapy had a significant impact on the recruitment of subjects for the study. The authors, in noting that their study showed effects which were statistically significant but of questionable clinical importance, called for further studies to "identify the patient population most likely to benefit from this treatment". This suggested that they believed that population heterogeneity had affected their results.

Yajnik et al.'s randomized trial of phenytoin for cancer pain involved 75 patients with ages from the twenties to over 60, and with primary cancer diagnoses involving 13 sites. The subjects were randomized to one of three treatment groups, with 25 per group, but some imbalance resulted - there was only one patient with pancreatic cancer, two with gall bladder cancer, two with ovarian cancer and one with thyroid cancer. Both patients with esophageal cancer were assigned to the same group. The investigators did not report the mechanisms of pain experienced by the subjects in the study, but did restrict entry to those with moderate to severe pain, based on an initial measurement with a visual analogue scale, and commented that the three groups were, as a result, comparable with respect to severity of pain.

Five other studies demonstrated the potential for population heterogeneity to affect a palliative care study,

although the authors did not address the existence or implications of heterogeneity and perhaps the issue was not relevant to their studies. Lubin, in a retrospective study to determine whether hospitalized patients could have received care at home, reviewed the charts of 96 palliative care patients after they had died³⁶. The population studied included a wide variety of diagnoses - 86% cancer, 10% heart disease and 4% AIDS. Ramsay's paper reported a retrospective, single cohort study of 26 referrals from a palliative care unit or day hospice to a liaison psychiatrist over a one year period³⁷. The study population was described as consisting of patients with the following characteristics: an age range of 30 to 79 years (median 60); a mixture of primary, terminal diagnoses including 25 with eight different categories of cancer and one with a non-cancer diagnosis; a wide range of illness durations ranging from one month to 31 years (median two years); various times since recurrence of disease or onset of serious complication, extending from one month to seven years (median six months); and a survival after referral from one week to 13 months. Twelve patients out of 26 had a previous psychiatric history. Although the results presented were descriptive, she looked at subgroups of the study population too, particularly with respect to survival. Pannuti et al. described retrospectively the first six years of their hospital-at-home project for advanced cancer patients. A total of 5603 patients were described, with ages ranging from four to 99 years (mean 70) and diagnoses spanning 32 primary cancer sites plus unknown primary cancers. The heterogeneity that existed between patients with different cancer diagnoses was demonstrated by the different amounts of time spent in home care and by their different survival times, even when performance status was considered. Lung cancer patients with the worse performance status survived a median of 14 days from the start of home care while breast cancer patients in the same category survived a median of 86 days.

Two time series studies, both mentioned earlier with respect to other obstacles, showed heterogeneity in their study sample, despite the small sample sizes used. In Walsh et al.'s report of patient controlled analgesia involving nine subjects, there was an age range of 40 to 73, six different primary cancers were represented, and several different pain mechanisms were present, with some patients having two or three mechanisms for their pains. The patients had four different indications for starting the sub-cutaneous morphine infusions and they received various other treatments prior to and during the study, including other medications and radiotherapy. In Walker's study of 15 patients in which a pain control leaflet was evaluated, the study sample was made up of patients who were between 37 and 84 years of age, had used sustained-release morphine for a period of time ranging from one day to four years, and were using morphine at a dose of between 10 mg and 1400 mg per day. As discussed earlier, the disease and symptom severity varied within this group.

Lack of Relevant Outcome Measures

Higginson et al. made the following comments in their article:

Outcomes for palliative care need to reflect the specific goals of care, such as improving the quality of life before death, controlling symptoms and supporting the family. Evaluations of palliative care have used a range of measures ... Measures were not standardized or tested for reliability or validity and reflected the aims of the particular study rather than the wider aims of palliative care.

Their study was one of a series of studies to develop and validate a new and relevant outcome measure for palliative care.

Deschamps et al. discussed the complexity of evaluating patients with cancer pain, with acute and chronic components, multiple sites, multiple etiologies, and its multidisciplinary

nature. In their study they used two methods of quantifying the patients' pain (performed nine times per day), asked the patients' their preference regarding therapy at the end of the second phase of the crossover, asked about side effects using a checklist and rating scale, and recorded the use of breakthrough doses of opioid. Multiple outcome measures were used in several other studies as well. In the study by Sciortino et al., a time series trial of the effect of blood transfusions on terminally ill cancer patients cared for at home³⁸, the investigators were interested in the potential physical and psychosocial effects. To accomplish this they assessed hematocrit, blood pressure, pulse, respiratory rate, cardiac function for signs of heart failure, shortness of breath, performance status, cognitive functioning, the amount of psychological distress, and quality of life (the latter done by the patient and by the social worker).

Power et al. felt that the depression scales that existed were not applicable to the terminally ill because they included somatic symptoms, which, in this population, could be secondary to the terminal illness. They stated: "There is no currently recognized method for assessing depression that is validated and standardized and designed to accommodate terminally ill cancer patients." For this, and other reasons discussed previously, they modified an existing instrument for use in their study. Keizer et al. were affected by the lack of appropriate tools for use in a palliative care study to assess satisfaction with care using telephone interviews with carers six to twelve months after the death. They dealt with this by creating their own 64 item questionnaire, which included five open-ended questions. They acknowledged that further research was needed to test the validity and reliability of the instrument they used in this study. Burge assembled a seven item VAS instrument for his study of fluid status-associated symptoms in palliative care cancer patients, identifying items from a literature search and from surveys of

doctors, nurses and patients. His study included an evaluation of the reliability of the instrument. He was also limited in the measurement of the fluid volume status of dying cancer patients - the clinical effects of the advanced disease and the absence of a non-invasive 'gold standard' were seen as obstacles to this assessment, in addition to the ethical issues mentioned previously. He chose to use a combination of clinical and laboratory measures, based on studies performed with non-cancer subjects.

On a related issue, Pannuti et al. expressed concern that economic evaluations performed in palliative care may not be looked on very favourably compared with other clinical settings if conventional methods of carrying out the studies and analyses are used. He planned a future publication dealing with a cost-benefit analysis of his program. Higginson et al. raised the same spectre of health technology assessments eventually looking at palliative care, stating that "high-quality palliative care can be expensive, and evidence of its benefit will be needed to warrant extension - and continuation." They saw their STAS instrument as an outcome measure which could be used in such evaluations.

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