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**THE USE OF ANTICHOLINERGIC AGENTS TO TREAT
EXCESSIVE OROPHARYNGEAL AND TRACHEAL
SECRETIONS IN PALLIATIVE CARE**

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Doctor of Philosophy

ASTON UNIVERSITY

December 2005

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**THE USE OF ANTICHOLINERGIC AGENTS TO TREAT EXCESSIVE
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Christine Ann Hirsch

Submitted for the degree of Doctor of Philosophy, 2005

Thesis Summary

Palliative care involves a multi-professional team approach to the provision of active, holistic care for patients and their families when the patient's disease is no longer responsive to curative treatment. Patient care encompasses medical and pharmacological intervention for symptom control, together with psychological, spiritual and social support for patients and families. Care is provided by teams in hospice, hospital or community environments. Although traditionally associated with providing care for cancer patients, palliative care services are increasingly providing for patients with non-malignant disease.

Symptoms commonly associated with terminal phase of disease include pain, nausea, agitation, respiratory symptoms and general fatigue. During the last few days of life, patients may become weak, resulting in difficulty taking oral medication and have periods of unconsciousness. Some patients may require drug administration via subcutaneous infusion. A proportion of patients may develop difficulty clearing respiratory secretions causing a characteristic 'death rattle', which although not generally considered to be distressing for the patient, is often treated with a variety of anticholinergic drugs in an attempt to reduce the 'noisy breathing' for the benefit of relatives and others who may be closely associated with the patient.

This study examined treatment of death rattle in two Hospices focussing on objective and subjective outcome measures in order to determine the efficacy of anticholinergic regimens in current use. Qualitative methods were employed to elicit attitudes of professionals and carers working closely with the patient.

The number of patients recruited and monitored were small, many confounding factors were identified which questioned firstly the clinical rationale for administering anticholinergic drugs routinely to treat death rattle and secondly, the ethics of administering drug regimens to patients to treat death rattle with the primary aim of relieving distress for others.

Ethical issues, including those of consent are discussed in relation to their impact on the methodology of end of life studies in medicines management in palliative care.

Key words: Palliative care, hyoscine, death rattle, glycopyrronium, anticholinergics

Dedication

I would like to dedicate this thesis to the memory of my mother Doreen Emily Burman.

Acknowledgements

Support from my academic and practice supervisors has been paramount in the progress of this research and production of the thesis. In particular I would like to thank my academic supervisor Dr John Marriott for his support and guidance, and Dr Christina Faull for her advice and encouragement.

Thanks also to Dr Ian Back for discussion and to the West Midlands Palliative Care Physicians for their support.

Thanks go to all the staff at the hospices who collected data and took part in the focus groups and to Dr Debbie Pearson for her ongoing support during this project.

Friends and work colleagues have been very supportive, in particular Dr Ann-Marie Bathmaker for her support and advice, Dr Celia Brown for statistical advice, and Robin Biles for database and computer support, Neil Hillman for advice on sound measurements, Frank Herold for his assistance in translating a paper and Dr Chris Langley.

Finally thanks to my family, Mark, Amy and Morgan, for their patience, support and encouragement.

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1 Background and preface to the Thesis

1.1 Preface to the arrangement of the text of this Thesis

The text of this Thesis is arranged over 10 Chapters. The background and introduction, in Chapters one and two, introduce and explain the term 'death rattle' in the context of palliative care in the UK and also explore the proposed causes of death rattle together with the historical and current use of anticholinergic drugs administered with the aim of reducing the death rattle symptoms. The aims of this study are explained in Chapter 3.

The 'literature review' of previous work exploring the use of anticholinergic drugs in the treatment of death rattle is presented as a systematic review, the results of which are presented in Chapter 5. The methodology for the systematic review, and all methods used within this study, is reported in Chapter 4, together with descriptions of the development of the methodology for evaluation of the anticholinergic treatments used to treat death rattle and qualitative methodologies used for relative interviews and focus groups with health care professionals.

The results gathered for each section of this study are then presented in separate chapters, followed by a discussion focussed primarily on the results from each component of the thesis as follows: Chapter 6 describes the outcomes from the developmental work with medical and nursing staff on issues of ethics, recruitment and consent. Chapter 7 reports firstly the results of the validation of the noise meter used for objective measurement of death rattle sound and secondly presents background demographical data and the results following the monitoring of patients who received anticholinergics for death rattle.

The qualitative results from interviews with relatives and focus groups with healthcare professionals are presented in Chapters 8 and 9 respectively. The relevance of results as a whole are then discussed together in the context of treatment of the patient with death rattle in Chapter 10.

1.2 Definition of palliative care and terminal care

Palliative care has been defined as

‘an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual’

(World Health Organisation, 2005).

Management of physical symptoms using drug therapy, forms only part of this holistic care but carries with it inherent risks and benefits. Symptoms experienced by terminally ill patients are variable and often multiple. Pain, nausea and vomiting, constipation, incontinence, general weakness and discomfort are commonly associated with the advanced stages of malignant and non-malignant diseases (Faull and Woof, 2002).

Terminal care is another term used to describe care provided for this group of patients. More specifically terminal care refers to

‘the management of patients during the last few days, weeks or months of life, from a point where it becomes clear that the patient is in a progressive state of decline’

(National Council for Hospice and Specialist Palliative care services, 1995).

When the patient enters the ‘terminal phase’ of their illness, also referred to as the ‘last 48 hours’ (although it may often be for longer or shorter time periods), other physiological changes occur. Patients may become increasingly weak, and may have periods of unconsciousness. This deterioration, although usually anticipated, can be most distressing for carers and relatives. Symptoms typically associated with this phase may include pain, breathlessness, restlessness and confusion, noisy breathing (commonly called ‘death rattle’) shortness of breath, nausea or vomiting, myoclonus, epilepsy and difficulty swallowing (Adam, 1997).

1.3 Treatment options in terminal care

The range of drugs commonly used to treat symptoms in the terminal phase is relatively small. Opioids together with adjuvant analgesics (non-steroidal anti-inflammatory drugs, antidepressants and anticonvulsants) may be combined to target pain of different origins. Anti-emetics (cyclizine, haloperidol, metoclopramide and levomepromazine) are used according to the underlying cause of the nausea and vomiting. Midazolam is commonly used as an anticonvulsant and to treat terminal restlessness and myoclonus.

Where patients develop noisy breathing, commonly referred to as 'death rattle', anticholinergic agents such as hyoscine hydrobromide, hyoscine butylbromide or glycopyrronium bromide may be prescribed.

The National Cancer Plan 2000 (Department of Health, 2000) required formalisation and improvement in the coordination and quality of services to enable people to die at home. Within this, guidance from the National Institute for Clinical Excellence (NICE) on Supportive and Palliative Care (NICE, 2004) recommended that Primary care teams should institute mechanisms in order to ensure assessment of patient's needs at this stage of their illness. This information should then be communicated within the Primary care teams using a system described as the Gold Standards Framework (GSF) (Thomas, 2003a; Thomas, 2003b). The GSF uses the mnemonic of the seven 'C's to illustrate the important components of the Primary care team's input to achieve the best care for dying patients and their families. One of the seven 'C's' referred to in the Framework stands for 'Care in the dying phase' and here the Liverpool Care Pathway for the Dying Patient, produced by the Liverpool Marie Curie Centre (Ellershaw and Wilkinson, 2003) is recommended by NICE as one method of providing a protocol driven pathway of care. The pathway addresses physical, emotional and spiritual needs in the dying phase and directs that a small range of drugs for symptom control should be prescribed by the General Practitioner for the patient to have in their home in anticipation of need during the terminal phase. Specifically drugs are prescribed in case the patient experiences pain, nausea or

agitation and recommends the prescribing of anticholinergic drugs for 'death rattle' on an 'if required' basis.

Many patients at this stage of their illness have difficulty swallowing, or may have reduced consciousness. Drugs are therefore often administered by continuous subcutaneous infusion via a portable battery operated syringe driver. The most commonly employed type of syringe driver used in the UK currently is the Graseby MS26 model.

1.4 Environments for delivery of palliative care

An appreciation of the different care settings in which palliative care occurs is necessary, as the place of care may have an influence on both the therapy required by the patient and that prescribed or administered by healthcare staff. It is well recognised that specialist palliative care in-patient units in the United Kingdom can provide care for only a small proportion of patients with terminal illness. The palliative care units employ a high proportion of trained, specialist staff forming the palliative care team. The team usually includes medical consultants or higher trained medical associates, registrars and other training grades of doctors, together with nurses, physiotherapists, social workers, pharmacists and other support staff. Most patients will be cared for at home by their General Practitioners or in hospitals.

Training of medical students in palliative care has only relatively recently become part of the syllabus requirement at Birmingham Medical School and included as part of the Regional vocational training for General Practice Registrars. Prior to this, medical training in palliative care was dependent on individual experience. Responses from 54 General Practice Registrars surveyed on their use of local symptom control guidelines indicated experience in palliative care ranging from very little to several weeks in a specialist palliative care unit during their training (Hirsch et al, 2000). Support for patients and advice for General Practitioners in the community has been available through the Hospice teams, or from specialist palliative care nurses who may or may not have varying degrees of specialist

medical support. The recent initiative provided through the GSF and the end of life care pathway being implemented in hospitals and community throughout England and Wales should improve palliative care provision by generalists and provide the opportunity to share examples of good practice (Murray et al, 2004).

1.5 Study Rationale. Hospice use of anticholinergic agents for the treatment of death rattle in the West Midlands

Following a survey of drugs administered by continuous subcutaneous infusion in the West Midlands Region (Hirsch, 1998), it was evident that different treatment regimens for death rattle were being employed across the Region. The survey was designed as a preliminary exercise prior to the development of drug compatibility charts to assist medical and nursing staff in their prescribing and administration of combinations of drugs by continuous subcutaneous infusion. The data collected also assisted in planning stage for a study to provide compatibility data which was not currently available

The procedure for setting up the infusion involves drawing up the required dose of drug or drug combination into a 10ml, 20ml or 30ml plastic Luer-lok syringe. The syringe is attached to the giving set, which is primed with the contents of the syringe. The syringe is then placed into the syringe driver. The needle on the giving set is placed subcutaneously in suitable site, usually on the patient's upper arm. Once started the syringe driver provides a continuous subcutaneous infusion by compressing the plunger of the syringe, over 24 hours (West Midlands Palliative Care Physicians, 2004).

The survey took the form of a retrospective review of prescription charts conducted in two hospices and a prospective survey in one hospice in the West Midlands Region. During this data collection, informal communication was made with palliative care staff encountered, based both in hospices and the community

in order to raise awareness of the task under review and gather further background information.

The survey results, together with the informal communication with hospice staff demonstrated that although many drug combinations and doses for pain, nausea, vomiting and agitation followed a similar pattern between hospices, the choice of anticholinergic agent used to treat death rattle, the dose prescribed, and the method of administration varied, between hospices. Confirmation of this variability was supported by discussion with Palliative care Consultants at a Regional meeting where support was given to pursue these investigations further.

Owing to practical considerations, this study concentrated on the variation in the treatment of death rattle administered to hospice in-patients between specialist hospice in-patient units in the West Midlands Region. At the start of the study, it was considered that data collected from the specialist units should reflect current best practice in treatment of death rattle.

1.6 Development of research questions

Consultation with different grades of nursing staff based in the hospices demonstrated that opinion seemed to vary with regard to effectiveness and benefits of anticholinergic agents for treating death rattle. Opinion from the literature indicated that death rattle itself was not generally thought to cause great distress to the patients, who were often not considered not to be fully aware of this symptom during the terminal phase of their illness (Bennett, 1996). Any benefits from anticholinergic treatment or other supportive measures were therefore likely to be experienced mainly by those relatives, or carers attending the patient with death rattle, for whom it is considered that the sound of death rattle can cause considerable distress.

Evaluation of the treatment of this symptom on a risk to benefit basis raised the following questions:

- What, if any benefit does the patient gain from such treatment?
- What, if any harm is there to the patients in view of the known toxicities of anticholinergic agents?
- Is it ethical to give drugs to one individual for the benefit of others?
- How evidence based is our current treatment of this symptom?

2 Introduction

2.1.1 Patients with cerebral and lung

2.1.2 Excessive oropharyngeal death rattle

2.1 Terminology: oropharyngeal and tracheal secretions or 'death rattle'

Several different terms have been adopted to describe the sound referred to and widely recognised as 'death rattle'. Ellershaw and co-workers (1995) used the term 'respiratory tract secretions' rather than death rattle and defined this as

'the sound audible at the bedside produced by movement of secretions in the hypopharynx or the bronchial tree in association with respiration.'

Bennett (1996) used the term 'noisy ventilation' referring to death rattle, a term which does not carry with it the association of death, and would therefore perhaps be a more sympathetic term to use when talking to patients, relatives and non-healthcare professionals about the symptom. The title of the present study initially used the term excessive 'oropharyngeal and tracheal secretions in palliative care' and this title was included on submissions to Ethical committees and in patient information leaflets. The symptom was described in terms 'noisy breathing' or 'chest rattle' when talking to patients and relatives about the study.

In view of the fact that the present study addressed the sound caused by these secretions in the last few days or hours of life, rather than at any other time of the illness, the term 'death rattle' was adopted for the purposes of writing this thesis.

2.2 Postulated causes and incidence of death rattle

Death rattle occurring during the 'terminal phase', is reported to occur in between 23% and 92% patients dying in hospices (Back and Jenkins, 1997; Back et al, 2001; Ellershaw et al, 1995; Higginson, 1999; Hoskin and Hanks, 1998; Hughes et al, 1996; Kass and Ellershaw, 2003; Lichter and Hunt, 1990; Power and

Kearney, 1992; Wildiers and Menten, 2002). Patients with cerebral and lung tumours were identified as being at particular risk of developing death rattle (Morita et al, 2000). More recent studies have confirmed that lung cancer seems to increase the risk of developing this symptom. In addition, a prolonged dying phase and male gender were associated with a higher risk of developing respiratory tract secretions (Kass & Ellershaw, 2003) as have pneumonia and dysphagia (Morita et al, 2004).

It is thought that secretions, produced by the salivary glands and bronchial mucosa, accumulate in the oropharynx and bronchi when the patient loses their swallowing and cough reflexes because of fatigue and weakness. Pooling of secretions is accentuated when the patient is in a supine or semi-recumbent position. The 'rattle' is produced by turbulent air flow through or over these secretions. In seeking to treat this symptom, pharmacological intervention has been aimed at reducing salivary and bronchial secretions. Air flow turbulence is affected both by ventilatory rate and airways resistance. Ventilatory rate may be reduced by sedative drugs such opioids or benzodiazepines widely used in the terminal stages of palliative care and airways resistance could be altered by the administration of beta agonists (Bennett, 1996).

2.3 Pharmacological regulation of oropharyngeal and respiratory secretions

2.3.1 Pharmacological regulation of saliva

Pharmacology texts report that salivation is under muscarinic control via acetylcholine in the parasympathetic nervous system. The muscarinic receptors have been classified into subtypes, M₁, M₂ and M₃ (Goyal, 1989). The administration of the antimuscarinic agent atropine causes a dry mouth at low doses (Rang, Dale and Ritter, 1999). Atropine, administered by inhalation, intramuscular injection and orally to nine patients with asthma, chronic bronchitis and bronchiectasis who produced large amounts of sputum was shown to reduce

sputum volume in two patients. The reduction in salivary secretion was felt to be the significant factor, causing patients to have dry mouths and difficulty in coughing up phlegm from the back of the throat (Lopez-Vidriero et al, 1975a). The extent of effectiveness of anticholinergic treatment in the production of excess saliva is difficult to establish. Jongerius and co-workers, (2003) carried out a systematic review for evidence of efficacy of anticholinergic drugs to treat drooling. Although there was evidence that three anticholinergic drugs (benztropine, glycopyrronium and benzhexol) were effective in the management of drooling, no conclusion could be drawn as to whether one drug was preferable to others.

2.3.2 Pharmacology of regulation of airways mucus secretion

Respiratory passages are kept moist by a layer of mucus, a dilute aqueous solution containing electrolytes, mucins (glycoproteins) and enzymes. The mucus is secreted partly by surface epithelial goblet cells lining the passages and partly by mucous cells of the submucosal glands.

The mucus exists as two layers, an upper layer which traps inhaled particles and a lower layer in which the cilia beat. The efficiency of mucociliary clearance, upward towards the pharynx propelled by the cilia, is determined by the physical properties of the mucus layer which can be impaired when the rheological properties such as volume and viscosity of the mucus increase or change. Secretion of mucus is under neuronal control (Rogers, 2001).

Bronchial secretory glands are known to be innervated by cholinergic nerve fibres although other factors such as adrenergic stimulation and inflammatory changes are also thought to stimulate the glands (Kaliner et al, 1986; Nadel, 1985; Lundgren and Shelhamer, 1990). In the respiratory tract, M3 receptors have been identified in the large airways. In the peripheral airways M1 receptors are also present. Recent studies have confirmed that parasympathetic (cholinergic) pathways are the dominant motor control of mucus secretion in humans, interacting via muscarinic M3 receptors to increase mucus output. Sympathetic (adrenergic) control of mucus secretion has not yet been demonstrated in human

airways although it is apparent in experimental animals (Rogers, 2001). Adrenergic nerve fibres are associated with human bronchial submucosal glands. In vitro human studies with human bronchi have demonstrated only a small increase in mucus secretion after adrenoreceptor stimulation (Phipps et al, 1982).

A third route of innervation, 'non-adrenergic non-cholinergic' (NANC) control has also been recognised. NANC is a pharmacological description of the innervating mechanism remaining after adrenoreceptor and cholinceptor blockade. NANC comprises many different neurotransmitting substances, including vasoactive intestinal peptide (VIP), substance P, neurokinin A, and nitric oxide. The combinations of transmitters are species specific. Chemosensitive C-fibres may be implicated in mucus hypersecretion (Belvisi, 2002). Two muscarinic receptors have been localised to human submucosal glands, M_1 and M_3 . M_3 seems to mediate mucus secretion whereas M_1 together with M_3 may control water secretion. The M_2 type muscarinic receptors are thought to inhibit acetylcholine release, performing a homeostatic role in mucus secretion in animals. Nitric oxide and VIP also seem predominantly inhibitory, having a regulatory action on neurogenic secretion (Rogers, 2002). It is thought that the NANC neural system regulates the activities of the autonomic nervous system with regard to airways secretions. The volume and composition of the mucus is likely to be under the control of different interlinking neural systems (Rogers, 2001).

Other agents which have been found to modulate mucus secretion in airways include the opioid drugs which interact with opioid receptors on the terminals of cholinergic and sensory afferent nerve fibres (Barnes et al, 1990). Morphine was found to inhibit capsaicin-induced mucus output in human bronchi *in vitro*, an effect which was reversed by naloxone (Rogers & Barnes, 1989). Opioid analgesics are commonly used in palliative care patients .

It is thought that abnormalities in the neuronal control of mucus secretion may contribute to the pathologies of conditions associated with mucus hypersecretion such as chronic bronchitis and asthma (Rogers, 2001). Mucus hypersecretion may have an acute onset for example in an acute asthma attack and is thought to occur when the secretory cells are activated. Mucus hypersecretion may also be a

chronic phenomenon for example in chronic lung conditions such as chronic bronchitis. In such conditions the goblet cells increase in number resulting in mucus which is more difficult to remove by mucociliary clearance or cough (Lundgren and Shelhamer, 1990). Cigarette smoking may also have a similar effect. As dying patients may often include patients in this category, it is probable that underlying multiple pathology may predispose some patients to be at greater risk of developing 'death rattle'. The complexities of control of mucus secretion in the airways suggests that death rattle may have many potential underlying causes involving different pharmacological pathways.

2.3.3 Rationale for the use of anticholinergic drug therapy to treat death rattle in palliative care.

Bennett (1996) hypothesised two distinct physiological mechanisms resulting in two different causes for 'death rattle'. The first, 'type 1', in which predominantly salivary secretions accumulated near to death, was proposed to be due to a loss of swallowing reflex. This type of death rattle occurring commonly during the last few hours of life, was felt to be unpredictable in nature. The second 'type 2' death rattle, was postulated to be caused mainly by accumulation of bronchial secretions over a period of several days, as the patient became too weak to cough effectively.

Bennett (1996) went on to propose that each type of death rattle required different management, anticholinergic treatment being most appropriate for 'type 1' and less effective for 'type 2'. Patients with 'type 2' death rattle appeared to demonstrate a lack of response to established infusions of hyoscine in addition to intermittent injections (Power and Kearney, 1992; Ellershaw et al, 1995). Bennett (1996) also suggested that patients with 'type 2' death rattle had additional physiological mechanisms such as an infective process, or hypoxaemia which may induce a reflex increase in bronchial secretions that are resistant to hyoscine treatment. Drug treatments addressing these alternative mechanisms may prove more helpful in these patients.

Morita and co-workers (2004) has more recently expanded on Bennett's hypothesis that the aetiology of death rattle is multiple and that differential diagnosis may be difficult. They (Morita et al, 2004) concurred that 'type 1' death rattle may be caused by a combined syndrome of aspiration owing to dysphagia and inability to expectorate, where as 'type 2' death rattle is more likely to be caused by an inability to expectorate an increased quantity of pulmonary secretion from tumour, infection, oedema or bleeding.

Neurogenic pulmonary oedema (NPE) has been highlighted as being a cause of 'intractable death rattle resulting sometimes in copious amounts of frothy secretions and pronounced death rattle which is unresponsive to traditional antisecretory medication or positional change. The mechanism for developing NPE is uncertain, but it is suggested that that this may be a more common cause of death rattle in palliative care than is currently recognised (Macleod, 2002).

It is clear that using anticholinergic agents to treat death rattle caused by 'type 2' is likely to be unsuccessful.

2.4 Therapeutic use of anticholinergic drugs in 'death rattle'

2.4.1 Anticholinergic drugs currently used to treat death rattle

Several audits have produced descriptive data on patient populations and the use of anticholinergic drugs to treat death rattle (Bennett, 1996; Hughes et al, 1996; Hughes et al, 2000). However the inherent problems of conducting research in palliative care, discussed in Sections 10.2 and 10.3, leave many unanswered questions about the efficacy of anticholinergic drugs in treating death rattle in these patients. Few studies have attempted to prospectively evaluate the efficacy of anticholinergic treatment and those that have, show limitations in study design such as variability in the definitions and quantification of death rattle or outcome measures as described in the critical evaluation of the literature (Chapter 5).

Recommended treatment for death rattle can readily be found in both specialist palliative care texts and increasingly for the non-specialist healthcare professional in general guidelines available in the United Kingdom in hard copy and on intranet websites (McMorran et al, 2005; British National Formulary Joint Formulary Committee, 2005; Twycross et al, 2002)

Texts and guidelines routinely used by palliative care specialists currently advocate repositioning of the patient and oropharyngeal suction (occasionally) (Bennett et al, 2002) plus drug therapy with one of three anticholinergic agents: Hyoscine hydrobromide, hyoscine butylbromide or glycopyrronium, for the treatment of death rattle. Although several publications in palliative care journals have expounded recommendations for various guidelines for each of these agents, overall reported success of treatment remains between 54% and 80% (Morita et al, 2000; Bennett et al, 2002). Guidelines readily available to the non-specialist generally recommend drug therapy with anticholinergic agents.

2.4.2 Background pharmacology and pharmacognosy of the 'belladonna' alkaloids

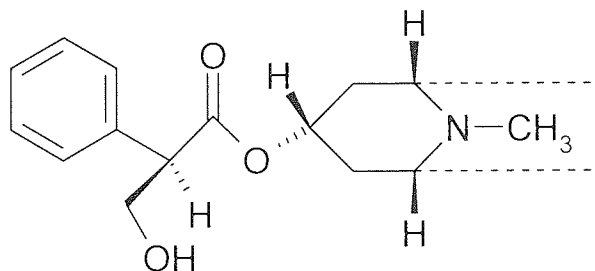
The belladonna alkaloids are derived from the solenaceae plant family, *Atropa belladonna* (Deadly nightshade), *Datura stramonium* (Thornapple; Jimson Weed) and *Hyoscyamus niger* (Henbane) (Evans, 2002). Hyoscine (scopolamine) is the ester of tropic acid and oscine (a more stable isomer of scopine). Atropine is the ester of tropic acid and tropine. Atropine is a racemic mixture of d-hyoscyamine and l-hyoscyamine, of which only the levorotatory isomer is pharmacologically active. Both atropine and hyoscine are competitive antagonists of the effects of acetylcholine at structures innervated by postganglionic cholinergic nerves. In very high doses atropine and scopolamine have local anaesthetic and ganglionic blocking properties (Greenblatt and Shader, 1973). Acetylcholine receptors are classified as nicotinic or muscarinic. As a group, the belladonna alkaloid compounds are often referred to as muscarinic antagonists, and thought to be non-selective at the different types of muscarinic receptors (Rang et al, 1999).

Preoperative anticholinergics were administered to patients undergoing anaesthesia to counteract the profuse sialorrhoea and vagally mediated bradycardia which was often induced by irritating gases used as general anaesthetics. Hyoscine (scopolamine) was often used in obstetrics because of its sedative and amnesic properties. Anticholinergic agents have also been employed for the treatment of gastrointestinal disorders, for vestibular disorders such as Menieres disease and motion sickness, in ophthalmology, and in the past as hypnotics. Anticholinergic drugs are also recognised to be beneficial in the treatment of Parkinson's disease (Greenblatt and Shader, 1973)

2.4.3 Atropine

Atropine is a tertiary amine (Figure 2.4.3) used less commonly nowadays as premedication to dry bronchial and salivary secretions in bronchoscopic procedures but retains an emergency role to treat vagotonic side effects.

Figure 2.4.3 Chemical structure of atropine



Atropine tablets are available for prescription for gastro-intestinal spasm. Other oral preparations containing atropine are available for purchase 'over the counter' by patients in the United Kingdom. Topical eye preparations of atropine are still widely used for mydriasis and cycloplegia. Atropine has rarely been described as a treatment for death rattle although it is prescribed to alleviate symptoms of excess saliva in palliative care, usually in the non-terminal phase in patients with Motor Neurone disease. The tertiary amines are lipid soluble, likely to cross the

of hyoscine hydrobromide was administered to subjects undergoing caesarian section, maximum serum concentrations of hyoscine hydrobromide were observed after 10 minutes and maximum heart rate was observed at 1 hour. An increase in subjective sedation at 30 minutes after the injection and anti-sialagogue effect did not occur before 30-60 minutes. There was no correlation between serum hyoscine hydrobromide level and heart rate response, or between the long lasting subjective sedation, the anti-sialagogue effect or the rapidly declining serum concentration (Kanto et al, 1989). This study demonstrated a rapid absorption rate from intramuscular injection but observed a much slower clinical response to the hyoscine hydrobromide. In contrast to atropine which is used to treat bradycardia in emergency situations, hyoscine hydrobromide produces bradycardia and central nervous system side effects are frequently seen resulting in drowsiness and amnesia (Ali-Melkkila et al, 1993). Repeated administration of hyoscine hydrobromide is reported to result in accumulation, occasionally resulting in paradoxical agitated delirium (Twycross et al, 2002).

Compared to other anticholinergic agents, data concerning the pharmacokinetics of hyoscine hydrobromide in man are limited. Hyoscine hydrobromide is readily absorbed from the gastrointestinal tract following oral doses. The oral bioavailability of hyoscine hydrobromide is reported to be between 60 and 80% (Twycross et al, 2002). Following oropharyngeal administration, the time to maximum plasma concentration is reported to be between 50 to 60 minutes (Ali-Melkkila et al, 1993). Hyoscine hydrobromide is almost entirely metabolised, a small proportion of the oral dose has been reported to be excreted in the urine (Ali-Melkkila et al, 1993). Plasma half life is reported to be between 5 and 6 hours and the duration of action as a spasmolytic is thought to be 15 minutes whereas the antisecretory effect is reported to have a duration of between 1 and 9 hours (Twycross et al, 2002)

Hyoscine hydrobromide is indicated for motion sickness and as a pre-medication for anaesthesia (B.N.F, 2005). Hyoscine hydrobromide is available as sublingual tablets which may be purchased 'over the counter' in the United Kingdom, for the treatment of travel sickness. Hyoscine hydrobromide injection is licensed for administration by subcutaneous or intramuscular routes (Martindale, 1999).

2.4.4.2 Transdermal hyoscine hydrobromide

Hyoscine hydrobromide is well absorbed following application to the skin and this has been exploited in the formulation of a transdermal hyoscine hydrobromide as a patch. The patch contains a priming dose of 140 micrograms of hyoscine hydrobromide (incorporated into the adhesive layer of the patch), together with a reservoir of 1.5mg hyoscine hydrobromide which delivers 0.5mg hyoscine hydrobromide a day, over 72 hours. The patch is usually applied to the postauricular area. The preparation was developed for the treatment of motion sickness. Side effects with this method of administration are as expected, dry mouth occurring in 67% of patients and drowsiness in 16% of patients, although there is some suggestion that this is comparatively less than with the oral preparations. Toxic psychoses have been reported in elderly patients (Clissold and Heel, 1985). The transdermal preparation of hyoscine hydrobromide is commonly used in palliative care to reduce excessive salivary secretions prior to the terminal phase, particularly in patients with degenerative neurological diseases such as Motor Neurone disease. Hyoscine hydrobromide patches are sometimes used in the community setting as a treatment for death rattle (Section 9.3.3.1).

The summary of product characteristics for Scopoderm TTS brand of transdermal hyoscine hydrobromide contraindicates the use of the patch in patients with glaucoma. The product information also cautions use of the patch in patients with pyloric stenosis, bladder outflow obstruction, intestinal obstruction, in the elderly, impaired renal or hepatic function. In rare cases, confusional states and cautions that hallucinations have been reported (Novartis, 2003). Hyoscine hydrobromide hydrolyses below pH 3, but is compatible with most drugs given by subcutaneous infusion used in palliative care (Trissel, 2003).

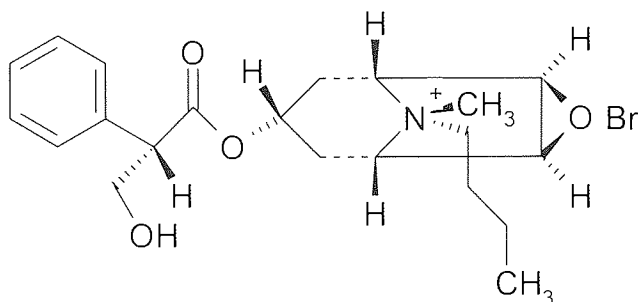
2.4.5 Hyoscine butylbromide

(Hunger Ingelheim Ltd, 1987)

Hyoscine butylbromide/bromide injection

Hyoscine butylbromide is a quaternary derivative of hyoscine which has poor oral absorption and does not readily cross the blood brain barrier (Figure 2.4.5).

Figure 2.4.5 Chemical structure of hyoscine butylbromide



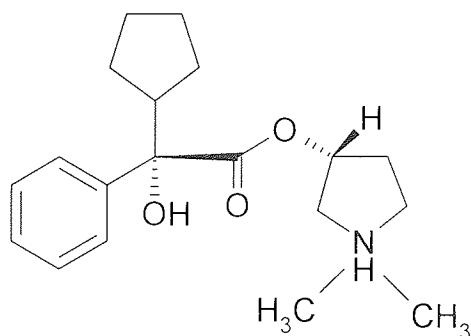
Central effects are therefore thought to be rare. Little work has been published on the pharmacology of hyoscine butylbromide. Herxheimer and Haefeli (1966) studied the effects of subcutaneous and oral administration in nine healthy volunteers on heart rate, salivary secretion and near-point accommodation. Hyoscine butylbromide was found to cause an increase in heart rate and inhibited salivary secretion but with short-lived effects, disappearing within an hour of giving the drug. Visual accommodation was paralysed, but in contrast to effects on heart rate and salivary secretion, the onset was slower but the effect persisted for 1 to 2 hours. The time difference between the peak effects on salivary secretion or heart rate and accommodation increased with increasing doses of hyoscine butylbromide, suggesting that the drug accumulated in a reservoir where it continued to be available to the ciliary muscles. It was postulated that hyoscine butylbromide was rapidly inactivated. Oral absorption of hyoscine butylbromide was found to be extremely poor. Twycross and co-authors (2002) however, quote antisecretory actions of 1 to 9 hours for both hyoscine butylbromide (and hydrobromide). Hyoscine butylbromide is licensed for the symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm. (B.N.F, 2005). Hyoscine butylbromide (Buscopan) injection is licensed for administration by

intramuscular or intravenous injection (Boehringer-Ingelheim Ltd, 1997). Compatibility data is available to allow the use of hyoscine butylbromide injection with most drugs commonly administered by subcutaneous infusion in palliative care (Hirsch et al, 2005).

2.4.6 Glycopyrronium bromide

Glycopyrronium bromide (Glycopyrrolate, USAN) is a synthetic quaternary ammonium anticholinergic agent synthesised in 1960 and used for the treatment of peptic ulceration (Figure 2.4.6).

Figure 2.4.6 Chemical structure of glycopyrronium



Later, in the 1970's, glycopyrronium was used during anaesthesia to reduce hazard of aspiration of gastric acid and as an adjunct to reversal by anticholinesterases of non-depolarising neuromuscular block. After injection, glycopyrronium was found to have a prolonged inhibitory effect on salivation and, in contrast to atropine, did not easily pass the blood brain barrier, causing fewer central effects. Mirakhur and co-workers (1978) studied the effects of different doses of glycopyrronium in six adult healthy volunteers, given in three different doses, intravenously (100, 140 and 200 micrograms), intramuscularly (100, 200, 400 micrograms) and orally (2,4,8mg). Measurements were taken at 30 and 60 minutes after administration, then hourly for 6 hours. There was great individual variation in salivary secretion before any drug was given. The effects of

glycopyrronium were greatest on salivary secretion and sweat gland activity. Higher doses of glycopyrronium tended to produce an earlier and more prolonged effect on salivary excretion, this being greatest with 200 micrograms of glycopyrronium suppressing salivary secretion between 1 and 2 hours after intramuscular injection, and 400 micrograms, intramuscularly reducing secretion further between 1 and 3 hours. An oral dose of 4mg of glycopyrronium reduced salivary secretion from 4 to 6 hours after administration, while 8mg reduced salivary secretion after 3 hours. Effects on pupil size and heart rate were minimal. Three out of six volunteers felt drowsy at different times after drug administration and headache was occasionally reported. The most consistently reported symptom was dryness of the mouth persisting for almost 24 hours after oral intake. Oral absorption of glycopyrronium was poor, requiring 35 times the parenteral dose to achieve a 50% reduction in saliva secretion. In a second volunteer study Mirakhur and Dundee (1980) compared atropine with glycopyrronium administered by intramuscular injection and found glycopyrronium to be five to six times more potent in inhibiting salivary secretion than atropine with minimal effect on cardiovascular, ocular and central nervous system when compared to atropine.

Mirakhur and co-workers (1980) studied the effect of intravenous administration of glycopyrronium and atropine administered intravenously in anaesthetised patients. A rise in heart rate was seen with both drugs although the time of onset was slower following glycopyrronium (3.7 minutes) compared to 2.6 minutes for atropine. Doses used in this study were based on weight resulting in some glycopyrronium doses being higher than used in the previous study (Mirakhur et al, 1978). Analysis of heart rate with varying doses of atropine and glycopyrronium was carried out in six volunteers (Ali-Melkkila et al, 1991). At low doses of atropine (120 micrograms) and glycopyrronium (50 micrograms) administered intravenously, bradycardia was only seen with atropine. At higher doses of atropine (720 micrograms) and glycopyrronium (300 micrograms) tachycardia was seen with both drugs.

Similar findings were reported by Ali-Melkkila et al, (1989) who studied the pharmacokinetics of glycopyrronium following intravenous, intramuscular and oral administration in 18 subjects undergoing ocular surgery. After intravenous administration, glycopyrronium was found to have a high clearance and low volume of distribution comparable to hyoscine hydrobromide. After intramuscular injection (8 micrograms per kg, into the deltoid muscle) absorption of glycopyrronium was fast with a mean time to maximum plasma concentration (t_{max}) of 27.48min. Although a mean maximum heart rate was observed after an hour, a peak anti-sialagogue effect observed at one hour (declining again at 2 hours), was not considered to be significant . The oral absorption of glycopyrronium was extremely variable, and poor (only a few percent of the orally administered dose). However oral administration of 4mg of glycopyrronium , which produced a minor effect on heart rate, showed anti-sialagogue effects 6 hours after administration, although the authors noted that the effect of fentanyl and diazepam used as adjuvants should also be taken into account.

Elimination of glycopyrronium is significantly prolonged in uraemic patients and it was concluded that the drug should be avoided in these patients (Kirvela et al, 1993).

Glycopyrronium injection (glycopyrronium 0.2mg per ml) is licensed for intravenous or intramuscular injection (Antigen, 1998). The injection has a pH of 2.3 to 4.3, and care must therefore be taken when combining drugs together for subcutaneous infusion, as above pH 6.0, the rate of hydrolysis increases significantly (Trissel, 2003).

Studies have also shown that glycopyrronium has a prolonged and significant bronchodilating action. (Gal & Suratt, 1981) In vitro studies showed that glycopyrronium was more potent than ipratropium in producing bronchodilation in lung tissue (Haddad et al, 1999).

2.4.7 Adverse effects and cautions with anticholinergic drugs

2.4.7.1 General anticholinergic side effects

All anticholinergic antimuscarinic agents can be expected to produce peripheral side effects including dryness of the mouth, resulting in difficulty swallowing and talking, and reduced bronchial secretions. In the case of treating death rattle, these may be regarded as 'desired' effects. Other side effects also occur: thirst; dilatation of the pupils (mydriasis); loss of visual accommodation (cycloplegia); photophobia; flushing and dryness of the skin. Atropine causes transient bradycardia followed by tachycardia (in contrast to hyoscine hydrobromide) with palpitations and arrhythmias. Patients taking anticholinergic drugs may also experience difficulty in micturition, reduction in tone and motility of the gastrointestinal tract, which may not be desirable in palliative care patients (Martindale, 1999).

2.4.7.2 Side effects specific to hyoscine hydrobromide

In contrast to atropine, hyoscine hydrobromide causes central depression at therapeutic doses causing symptoms of drowsiness and fatigue. Hyoscine hydrobromide may produce central nervous system (CNS) stimulation rather than depression at therapeutic doses, which may be more likely in patients with impaired metabolic liver or kidney impairment. Hyoscine hydrobromide appears to cause bradycardia. The manufacturers of hyoscine hydrobromide caution against general anticholinergic side effects but more specifically against excitement, confusional states, delirium, rashes and possible slowing of the heart, although these occur rarely.

2.4.7.3 Side effects specific to hyoscine butylbromide

Central side effects are generally rare with hyoscine butylbromide as the quaternary salt is unlikely to cross the blood brain barrier. However changes in

visual accommodation which persisted for one to two hours, were found to occur following subcutaneous injection of hyoscine butylbromide, the effect reaching a peak 5 to 30 minutes after maximum effects were observed on heart-rate and salivary secretion. It was postulated that this might be due to direct action of the drug to ciliary muscle rather than a special affinity for the receptors. This led to the suggestion that a reservoir of accumulated drug might exist, accounting for the long duration of this effect. Subcutaneous injection of hysocine butylbromide was found to increase heart rate (Herxheimer and Haefeli, 1966). As with other anticholinergic drugs there are cautions against the use of hyoscine butylbromide with prokinetic agents as there is the possibility of antagonism of actions (Twycross et al, 2002).

2.4.7.4 Side effects specific to glycopyrronium bromide

Like hyoscine butylbromide, glycopyrronium is less likely to cross the blood brain barrier. The summary of product characteristics for glycopyrronium includes the following side effects as an extension of its pharmacological activity: difficulty in micturition; disturbances in visual accommodation; tachycardia; palpitations and inhibition of sweating. Apart from hypersensitivity to glycopyrronium, there are no absolute contra-indications, however special warnings include use of anticholinergic agents generally in patients with coronary artery disease, congestive heart failure, cardiac arrhythmias, hypertension, thyrotoxicosis and in pyrexial patients due to inhibition of sweating (Antigen, 1998). An anecdotal report published on a palliative care bulletin board, reminds of the potential for side effects resulting from long term administration of anticholinergic agents when a patient developed paralytic ileus after glycopyrronium was administered by subcutaneous infusion for drooling caused by cancer of the tongue (Corkhill ,2004).

2.5 Differential diagnosis of death rattle. Importance in treatment

2.5.1 Differential diagnosis of noisy breathing or secretions

Although a definition of death rattle has been given (Section 2.1), the words define a sound, produced by the patient, rather than including any description or reference to the possible underlying cause. It is probable that other underlying conditions may result in a sound like 'death rattle'. When patients are referred for palliative care, by definition and referral criteria, their disease prognosis is relatively short. It is however, often difficult to decide when the patient is in their 'last 48 hours' of life. Other underlying conditions such as pulmonary oedema, respiratory infection, or other hypersecretory syndromes could cause a 'type 2' death rattle as described by Bennett (1996) which may not readily be distinguished from 'type 1' death rattle. Bennett's hypothesis of the existence of two types of death rattle, emphasises the need for closer attention to the differential diagnosis in order to determine the underlying aetiology of the death rattle symptom to allow the most appropriate course of treatment or intervention to be prescribed.

Anticholinergic drugs are also used in palliative care for reducing secretions in patients who are not in the dying phase. Occasionally patients with oral and oesophageal cancers have difficulty swallowing, a symptom also common in chronic neurological disease such as Motor Neurone Disease and Amyotrophic Lateral Sclerosis. Drooling is also reported in patients with physical or learning disabilities and can be caused by some of the newer psychiatric drugs. Anticholinergic drugs have been used as treatment in neurological conditions and drooling, however where the quality and life expectancy of the patient can be improved other options such as the injection of botulinum toxin into the salivary glands can prove successful. The rest of Section 2.5 explores different pathologies resulting in salivary and respiratory hypersecretion syndromes, treatments which have been used to address these symptoms and how this may relate to the treatment of death rattle.

2.5.2 Sialorrhoea, symptoms and treatment useful way to highlight research in

Sialorrhoea and drooling are not common symptoms in advanced cancer as many patients tend to suffer from dry mouth owing to disease or as a side effect of treatment with various drugs which often have anticholinergic side effects. These include the opioid analgesics, antidepressants and some antiemetics. There are some cancers however, such as oral and oesophageal cancers and those of the upper digestive tract where excess production of saliva and difficulty in swallowing make drooling a problem. Other conditions encountered in palliative care which require management of secretions include Amyotrophic Lateral Sclerosis, other forms of Motor Neurone disease, Multiple Sclerosis and Parkinson's disease.

Transdermal hyoscine hydrobromide patches have traditionally been used to treat drooling in this group of patients. Nebulised hyoscine hydrobromide injection has also been administered to treat dribbling in cases where transdermal hyoscine hydrobromide had not produced the desired response and more over had caused urinary retention. Two patients were subsequently given oral tablets of hyoscine hydrobromide 300 micrograms six hourly which had also failed to produce a response and had caused dizziness in one patient. Nebulised hyoscine hydrobromide 800 micrograms, administered two to three times daily, was found to be an effective treatment for dribbling as rated by the patients, with no reported side effects (three case studies) (Zeppetella, 1999). Nebulised administration of hyoscine hydrobromide was hypothesised by the author to have allowed rapid systemic absorption, but the fact that patients in the case studies had rapid onset of effect with no reported troublesome side effects suggested a local action of hyoscine hydrobromide on salivary glands. Two subsequent case reports reinforced the success of nebulised hyoscine hydrobromide, one in a patient with Amyotrophic Lateral Sclerosis and the second with squamous cell carcinoma of the mouth causing dysphagia. Dose titration was carried out to produce optimal reduction in secretions with minimal side effects of dry mouth. As no evidence of central or gastrointestinal side effects were seen, it was again concluded that the action of the hyoscine hydrobromide was a local one, on salivary glands. The author suggested that an *N* of 1 study with multiple crossovers between nebulised

saline and hyoscine hydrobromide would be a useful way to further research in this area (Doyle et al, 2000)

Oral glycopyrronium has also been reported to have been used successfully to treat drooling in an adult patient with oral cancer. A dose of 400 micrograms was administered orally three times a day, reducing drooling to an acceptable level with no reported side effects (Olsen and Sjogren, 1999). Another patient with oral cancer and drooling of saliva, receiving feeding and medication via a percutaneous gastrostomy tube, achieved a reduction in drooling following the administration of between 600 micrograms and 1mg glycopyrronium, titrated to response. Treatment continued for six months with no reported adverse effects (Lucas,1998). A case report describing the successful nebulisation of glycopyrronium for a patient with Motor Neurone disease was described (Strutt et al, 2002). A dose of 400 micrograms was nebulised twice daily and the patient reported an improvement in symptoms. The regimen was continued for two months before treatment was stopped because a rash, thought to be due to the glycopyrronium, developed around the mouth. The authors were not able to draw any conclusions on whether nebulised glycopyrronium was acting locally or systemically in this patient.

Much of the research surrounding drug treatment of drooling has been carried out in children. A systematic review of the evidence for the efficacy of anticholinergic agents in treating this symptom was carried out by Jongerius and co-workers (2003). Drug treatments identified were glycopyrronium, transdermal hyoscine hydrobromide, benztropine, and benzhexol with evidence of some effect with all of these agents. The review found difficulty in reaching a conclusion about the most effective treatment as no drug was evaluated systematically. The follow up period was not greater than a few weeks (although this would not be relevant to the patients in the present study) and no single method of measurement of salivary flow was used.

Other treatments commonly used to treat excessive drooling include the sublingual administration of atropine 1% w/w ophthalmic eye drops, particularly in patients with neurological disease. Anecdotal references to the successful use of

this formulation of atropine can be found on the palliative drugs bulletin board (Pacl et al, 2002). Eisenchlas (2003) reported that an analysis of a double blind randomised crossover trial of atropine drops v placebo in drooling patients with upper digestive cancer had shown no statistical significance between atropine and placebo. There was however a marked decrease in the impact of secretions noted by patients in both groups. No details of the trial were reported. Injection of botulinum toxin A into the salivary glands was found to be successful in a small pilot study in 5 patients to treat sialorrhoea in patients with Amyotrophic Lateral Sclerosis (Giess et al, 2000). Four out of the five patients found a marked reduction in salivary production over a three month follow up period following injection of botulinum toxin A into the parotid glands and if necessary the submandibular glands. The mechanism of action proposed was based on botulinum toxin A induced blockade of acetylcholine release at the cholinergic neurosecretory junction of the salivary glands. No adverse effects were reported, in particular, no drying of the mouth.

2.5.3 Bronchorrhoea, symptoms and treatment

Bronchorrhoea, the production of large amounts of frothy sputum, has been defined as the profuse production of sputum in which more than 100ml of sputum is produced within 24 hours. Bronchorrhoea has been observed in some patients with chronic lung diseases such as chronic bronchitis, chronic bronchiectasis and bronchioalveolar carcinoma (Homma et al, 1999). Bronchorrhoea has also been observed to occur as a complication of metastatic cervical adenocarcinoma (Epaulard et al, 2001) and pancreatic carcinoma (Lembo and Donnelly, 1995). The rheological and chemical characteristics of the sputum produced in terms of viscosity, dry weight, N-acetyl neuraminic acid (NANA), fucose and sulphate content differ between bronchorrhoea and hypersalivation. The levels of these constituents are higher in bronchorrhoea sputum than saliva and could therefore be used to aid differential diagnosis between bronchorrhoea and hypersalivation (Lopez-Vidriero, 1975b). Although likely to affect only a small number of palliative care patients, bronchorrhoea may be a potential underlying cause of death rattle in some patients.

The definition of bronchorrhoea describes the symptom rather than the underlying cause and various treatments have been used with the aim of relieving this symptom. The following treatments were suggested on the 'palliative drugs' bulletin board in answer to a request for information for treatment of bronchorrhoea: furosemide was cited, together with oral or inhaled corticosteroids, nebulised furosemide 20mg four times daily, macrolide antibiotics or nebulised indometacin corrected for pH (Wilcock, 2002).

Sputum production in a patient with gastrointestinal cancer-associated antigen (CA19-9) –positive bronchioalveolar carcinoma accompanied by bronchorrhea and respiratory failure reduced following treatment with high dose corticosteroids: methylprednisolone 1gram per day for 3 days followed by prednisolone 60mg per day (Nakajima et al, 2002).

Another report described two patients with bronchorrhoea, refractory to treatment with macrolides antibiotics and corticosteroids, who were treated with inhaled nebulised indometacin (2ml of an aerosol containing 25mg of indometacin in saline adjusted to pH 7.40) administered three to six times daily. A decreased sputum volume and symptomatic improvement of dyspnoea and hypoxaemia was reported as a result of treatment (Homma et al, 1999). The autopsies of these patients confirmed the origin of the mucus production to be malignant cells rather than hypertrophy of the bronchial glands and goblet cell hyperplasia of the bronchial epithelia. The proposed mechanism of production of the sputum was threefold: hypersecretion of mucus from glycoprotein producing cells; increased transepithelial chloride ion secretion plus excessive transudation of plasma products into the airway space (Lundgren and Shelhamer, 1990). Prostaglandins (PGE2 and PGF2 alpha) stimulate chloride secretion toward the lumen and hence promote water accumulation. Indometacin was proposed to act by reducing the synthesis of prostaglandins in the airways (Homma et al, 1999). Tamaoki and co-workers (2000) studied the effect of inhaled indometacin in seven patients with bronchorrhoea due to bronchioalveolar carcinoma on the expression of cyclooxygenase-2 (COX-2) messenger RNA (mRNA). The expression of COX-

COX-2 mRNA was detected in four patients. After 4 weeks of treatment with inhaled indometacin, the patients expressing COX-2 mRNA demonstrated a decrease in sputum production in comparison to the patients not expressing COX-2 mRNA. The authors postulated that upregulation of COX-2 in carcinoma cells with the resultant synthesis of cyclooxygenase product of arachidonic acid may be involved in the pathogenesis of bronchorrhoea and that blockade of COX-2 seemed effective treatment for this condition. Oral indometacin administered 25mg three times a day for 28 days did not show the same benefits in terms of reduction in sputum volume in a group of nine patients with bronchiectasis (Llewellyn-Jones et al, 1995). The authors postulated that this may be due to insufficient concentration of drug at the site of action, compared to that achieved with nebulised therapy. An inhibitory effect on peripheral neutrophil function was however observed. An alternative theory could be that the mechanism of sputum production is complex, requiring different therapeutic approaches in different disease states, and between different groups of patients with the same disease state.

Although infection has been included in the pathogenesis of mucus hypersecretion (Lundgren and Shelhamer, 1990) and would therefore seem to be a rational addition to therapy where an infective origin was suspected, Marom and Goswami (1991) published a case study in which a patient with bronchorrhoea responded to treatment with erythromycin where other antibiotics had failed to give any benefit.

One anecdotal report communicated the success of the administration of octreotide, 800 micrograms administered by subcutaneous infusion over 24 hours to a patient with inoperable carcinoma of the oesophagus without stenting. The patient was reported to be producing copious amounts of tenacious secretions daily. The secretions were reported to be reduced within 24 hours and remained so for two weeks until the patient's death (Postle-Hacon, 2005).

2.5.4 Cardiogenic pulmonary oedema as an underlying cause of death rattle

It is not clear how often the distinction of death rattle due to cardiogenic origin is identified in palliative care in order to choose the most appropriate therapeutic option to treat resulting death rattle. This condition has been recognised as 'not readily responding to hyoscine hydrobromide (scopolamine), glycopyrronium or atropine drops' together with 'loop diuretics, nitroglycerin and morphine' (Lagoski, 2002).

Although nebulised furosemide has anecdotally been reported to be beneficial in reducing excessive secretions due to pulmonary oedema (Knower, 2004) and implying that the nebulised route is an alternative to oral or intravenous administration, the precise outcome measured in this communication was unclear. Furosemide (20mg four times daily) administered via a nebuliser to three patients for the treatment of dyspnoea, resulted in symptom relief, without causing systemic effects of diuresis (Shimoyama and Shimoyama, 2002). Animal studies have demonstrated a local effect of furosemide, rather than systemic, implying activity on pulmonary receptors which are thought to mediate antidyspnoeic and bronchodilatory effects (Sudo et al, 2000). Barnes and co-workers (1990) postulated that furosemide may have direct activity on sensory nerves, preventing bronchoconstriction.

2.5.5. Neurogenic pulmonary oedema as an underlying cause of death rattle

Neurogenic pulmonary oedema may be a cause of 'treatment resistant death rattle' in the terminal phase of some palliative patients. The mechanism for developing neurogenic pulmonary oedema remains uncertain but is thought to be related to an abrupt increase in intracranial pressure, leading to respiratory symptoms which could be mistaken for aspiration pneumonia or be subclinical. Three cases were reported where the acute onset of death rattle due to neurogenic pulmonary oedema was suspected. The 'rattle' was resistant to anticholinergic therapy (Macleod , 2002).

2.6 Bronchodilatory agents which may affect death rattle

The bronchodilatory action of the belladonna alkaloids have long been recognised. Smoke produced by burning leaves of *atropa belladonna* was used in the past to relieve bronchospasm and asthma remedies containing extracts of *Datura stramonium* were available (Greenblatt and Shader, 1973). No longer used for this purpose because of the side effect profile, there are now available several anticholinergic agents specifically developed for their bronchodilatory effects with fewer systemic anticholinergic side effects. Although the desired pharmacological action of anticholinergic agents in the treatment of death rattle is to reduce oropharyngeal secretions, the bronchodilatory action of the anticholinergics may in some patients play a part in reducing the rattle noise by affecting airflow over the secretions.

2.6.1 Ipratropium bromide

Ipratropium bromide is a quaternary ammonium compound which has potent antimuscarinic activity but poor absorption from the respiratory tract, reducing the potential for anticholinergic side effects. Atropine depresses ciliary beat function and slows airway mucociliary clearance. Ipratropium seems to lack this effect. Ipratropium and atropine have similar action in blocking production of respiratory secretions in response to cholinergic stimulation, but have no effect on baseline secretions (Wanner, 1986). The duration of action of ipratropium as a bronchodilator is four to eight hours (Twycross et al, 2002) and there has been a search for similar compounds with a longer duration of action.

An in vitro study using human tissue, showed that glycopyrronium was more potent an inhibitor of cholinergic neural responses than ipratropium. Glycopyrronium was found to dissociate very slowly from human airway smooth muscle (HASM) muscarinic receptors compared to ipratropium which might explain its longer duration of action (Haddad et al, 1999). Bronchodilation produced by inhaled ipratropium was compared with glycopyrronium in vivo. Glycopyrronium was found

to have a much longer duration of action than ipratropium; up to 30 hours (Hansel et al, 2005). Ipratropium has not been studied in the treatment of death rattle.

2.6.2 Tiotropium bromide

Tiotropium is a recently introduced anticholinergic agent, only available as an inhaled powder. It provides prolonged blockade of the muscarinic M3 receptor for over 24 hours allowing once daily administration. The only significant side effect of inhaled tiotropium seemed to be dry mouth, reported in 10-16% patients (Gross, 2004). This agent is licensed only for maintenance treatment of chronic obstructive pulmonary disease and is not indicated for acute relief of bronchospasm (B.N.F, 2005).

Both ipratropium and tiotropium list dry mouth, nausea, constipation and headache as side effects, with tachycardia and atrial fibrillation also being reported. Tiotropium has not been used in the treatment of death rattle.

2.6.3 Salbutamol and Salmeterol

Although adrenergic control of respiratory secretions has been demonstrated in experimental animals, this has not yet been demonstrated in human airways (Rogers, 2002). Studies have suggested that beta 2-adrenergic agonists such as salbutamol and salmeterol may increase ciliary beat frequency. An in vitro study demonstrated a short lived increase in ciliary beat frequency in cultured human bronchial epithelial cells in response to salbutamol. A similar response but with longer duration of effect was seen in the presence of salmeterol (Devalia et al, 1992).

This ciliostimulating effect of salmeterol was confirmed (Piatti et al, 2005) and demonstrated when salmeterol was applied directly to epithelial samples obtained by nasal brushing in ten patients with chronic obstructive pulmonary disease (COPD) with community acquired pneumonia compared to eight healthy controls subjects and in COPD patients only. Salmeterol induced ciliostimulation in all the groups of patients

2.7 Other agents reported to have been used to treat death rattle

Possibly because of the poor and variable response of death rattle to treatment with traditional 'anticholinergic' drugs and the 'need' for the health care professionals caring for the patients to alleviate the symptoms for the benefit of patient and carers, other drugs and interventions have been used. Some of these reports have been published as case studies, others, of a less evidence based nature, appear on professional bulletin boards. The success reported with the variety of classes of drugs treatment, support a complex and variable underlying aetiology of death rattle.

2.7.1 Beta antagonist drugs

Propranolol, a beta 2-adrenoreceptor antagonist was used in a pilot study to control thick mucous secretions in patients with Amyotrophic Lateral Sclerosis. In a small (N=16) randomised uncontrolled trial, 12 (75%) of patients subjectively reported a decrease in secretion of thick tenacious mucus when taking propranolol 10mg twice daily or metoprolol 25mg twice daily. The four non responders noticed no change subjectively (Newall et al, 1996). Although neither of these agents have been used widely in the treatment of secretions in palliative care, the possibility of multiple mechanisms of control of respiratory secretions may require alternative therapeutic approaches.

2.7.2 Antibiotics

Spruyt and Kausae (1998), described the successful use of ceftriaxone in a case report of a patient diagnosed with advanced multiple myeloma, with mucoprurulent, copious secretions discharging from the mouth. No benefit resulted from administration of hyoscine hydrobromide. A single dose of ceftriaxone 1g was administered intramuscularly. Sputum discharge resolved within ninety minutes but

respirations remained noisy until death. This mode of treatment may be an option where infection was felt to be present.

2.7.3 Opioids

It is possible that some patients may derive unrecognised benefit from the effect of opioids, prescribed concomitantly for pain relief, on mucus secretion. Capsaicin induces release of neuropeptides such as substance P from sensory nerves. Capsaicin induced mucus secretion in human bronchial tissue *in vitro*, was inhibited by morphine, an effect which was reversed by naloxone (Rogers and Barnes, 1989). This mechanism was considered to be important in inhibiting abnormally stimulated mucus secretion, rather than mucus secretion under normal cholinergic control. It was suggested that opioids may subsequently not cause such troublesome drying side effects as atropine.

2.8 Evidence based treatment of death rattle in palliative care

Variability in many aspects of palliative care services have been identified, including the drug treatment regimens used for symptom control (Higginson, 1999). For evidence regarding the efficacy of drug treatment, the randomised controlled trial (RCT) remains the gold standard. The RCT compares the outcomes in a group of patients randomly assigned to receive the test treatment with outcomes observed in a comparable group of patients receiving a control treatment. The conduction of randomised controlled trials in palliative care however, poses many practical difficulties. Grande and Todd, (2000) reviewed the difficulties of carrying out trials in palliative care. The review focused on trials of palliative care services, perceiving those to be different from trials of drugs in palliative medicine, however in the field of studying existing drug therapy which has been used traditionally for many years, outside its licensed indication, many issues are similar:

The randomisation process itself poses problems in palliative care as the population being studied is felt to be a particularly vulnerable. In the case of a

treatment for death rattle however, it should be possible to randomly assign patients to one or another anticholinergic agent. The length of time available for a study of drug therapy at the end of life is limited, therefore a crossover trial would be unsuitable. Parallel group trials would theoretically be a suitable design, however the resources required for this were beyond what was available to a single researcher. Although the N-of-1 trial has been advocated as being useful, providing a high strength of evidence for making individual patient decisions (Tilling et al, 2005) and would be applicable to palliative care patients at an earlier stage in their disease, the time available to study the action of anticholinergic drugs in each patient is unpredictable and possibly in some cases very short.

Commonly palliative care patients are elderly, have multi-system disease, multiple drug therapy, together with varying rates of disease progression and a limited survival time. The rapidly progressing nature of the disease necessitates regular therapy review. Although the study of drugs in the treatment of death rattle is confined to the terminal phase of the patient's illness providing some selection criteria, any further restriction of inclusion or exclusion criteria could inhibit patient recruitment to the detriment of the study. The results of such a study also need to be applicable to the wide range of patients being treated and so should be reflected in the trial population.

The present study was planned and developed at the end of 1999. At this time there was little published literature regarding the treatment of death rattle (Lichter and Hunt, 1990; Power and Kearney, 1992; Lucas et al, 1994; Ellershaw et al, 1995; Bennett, 1996; Back and Jenkins, 1997). Two of these studies were retrospective reviews of patient case notes and medication records, one with the aim of assessing medication given in the final 24 hours of life (Power and Kearney, 1992) and one more specifically examining the use of hyoscine hydrobromide usage in the treatment of death rattle in the dying phase (Back and Jenkins, 1997). Lichter and Hunt (1990) had carried out a prospective observational study of symptoms occurring during the last 48 hours of life in palliative care patients, including an assessment of the frequency and use of hyoscine hydrobromide. Lucas and co-workers (1994) reported their experience of the use of glycopyrronium by subcutaneous infusion, in eleven patients for the

treatment of death rattle and found that glycopyrronium was suitable for subcutaneous infusion and may be more effective if started before secretions had accumulated. Ellershaw (1995) carried out a prospective study in order to assess the hydration status of the patient in relation to the development of respiratory secretions, symptoms of thirst and dry mouth and corresponding blood biochemistry results. Although the results suggested some association with hydration status and the development of respiratory secretions, these were not statistically significant. Back and Jenkins (1997) focused on the treatment of death rattle in more detail and in a prospective study piloted a categorical rating scale to assess the efficacy of hyoscine hydrobromide administered to treat death rattle. Over the course of this study further literature has been published (Hughes et al, 2000; Morita et al, 2000; Back et al, 2001; Likar et al, 2002; Wildiers and Menten, 2002; Kass and Ellershaw, 2003; Morita et al, 2004; Wee, 2003) and a more detailed review of this literature is found in Chapter 5.

Outcome measures in palliative care studies need to be sensitive to the intervention (Grande and Todd, 2000). It is recognised that data may be difficult to collect and may rely on assessment by proxy. Outcome measures often tend to be of a qualitative nature and therefore more difficult to define and standardise. It seems essential therefore to develop research methods, which withstand the scrutiny of rigour, reliability and validity but also meet with ethical requirements, and incorporate the sensitivity required to minimise any extra burden to the patient and relatives.

3 Aim of the study

To evaluate and establish the optimal antisecretory therapy that may be used to relieve the adverse effects of excessive bronchial secretions in terminally ill patients receiving palliative care within inpatient Hospices in the West Midlands

3.1 Objectives of the study

- Perform a systematic review of the evidence base supporting the use of antisecretory treatments for death rattle within palliative care.
- To validate a practical objective method to assess the effects of therapeutic intervention in patients with death rattle receiving palliative care.
- To establish the perspective of relatives or carers on death rattle and its treatment using face to face interviews in West Midlands Hospices
- To establish perceptions of medical and nursing staff on treatment of death rattle using focus groups.
- To make recommendations for death rattle antisecretory therapy best practice to be included in future guidelines.

4 Methodology

4.1 Introduction

The difficulties in conducting studies in palliative care have already been expressed in the introduction (Section 2.8). The following chapter describes the different methodologies chosen for each part of the present study and follows the development of the methods in order to accommodate the requirements of the patients, hospice staff and Ethical committees

4.2 A systematic review of existing literature on the use of anticholinergics to treat respiratory secretions in the terminal phase in palliative care

In order to retrieve previous studies on the use of anticholinergics in the treatment of death rattle published in the literature, a Medline search was conducted via PubMed using specific terms from the Medline thesaurus: cholinergic antagonists; muscarinic antagonists; atropine; hyoscine; scopolamine; glycopyrrolate; respiratory sounds; respiratory system; palliative care and terminal care from 1966 to the present. Free text searching using the term 'death rattle' was also used. Because of the lack of published data on this subject, searches were kept broad, using the terms palliative care or terminal care and combined with individual drug terms. The Pharmline database was searched using the terms hyoscine, atropine, anticholinergics, palliative treatment, secretions (with respiration), terminal care and glycopyrronium. This was repeated throughout the duration of the study together with prospective searching of palliative care journals contents pages via Zetoc, an electronic service providing access to the British Library's Electronic Table of Contents. Reference lists within the publications accessed were also followed up.

Grey literature searching in palliative care was carried out using two specialist palliative care on-line bulletin boards; 'Palliative Drugs' available at <http://www.palliatiivedrugs.org/pdi.html/> and 'Palliative Care Matters' available at

<http://www.mrw.pallcare.info/>. Searching for grey literature in palliative care has been reported not to add to the 'recall' of papers accessed via the overall search strategy at the current time (Cook et al, 2001). Personal contact was made however with clinicians working in palliative care, known to have an interest in this area with the aim of retrieving any non published studies. In particular, during the early part of this study, contact was made with a working party based at a Leicester hospice which had sent out a call for papers or work relating to the treatment of death rattle. The aim of this working party was to produce guidelines for the treatment of death rattle. No language was specified during the literature searching, one non-English paper was located and translated. The systematic review was conducted with reference to the guidelines set out by the Cochrane Collaboration (The Cochrane Collaboration, 2004) and Davies and Crombie (2001).

In view of the anticipated paucity of randomised controlled trials conducted in symptom control in palliative care, any studies accessed using the search terms where the title was directly related to the treatment of death rattle or symptom control in the last 48 hours of life in palliative care, were included in the review. The following criteria were reviewed for each study accessed: The type of study and whether this was prospective or retrospective, interventions studied, outcome measurements, entry criteria, endpoints of the studies, results including the appropriateness of statistical testing and subgroup analysis for possible additional risk factors for developing death rattle, the number of study centres involved and whether the report included reference to ethical issues.

As the majority of studies accessed were non-experimental in design, criteria suggested in order to critically appraise the validity of observational studies were applied by identifying sources of bias in selection, performance, attrition and detection (Green and Higgins, 2005). These criteria were examined for each study within the context of the study of death rattle at the end of life and subsequent methodological considerations. (The results are shown in Sections 5.1 and 5.2).

4.3 Development of methodology for evaluation of the efficacy of anticholinergic drugs in the treatment of death rattle.

An objective measure of death rattle was required to support subjective outcome measures of the success of anticholinergic therapy to treat death rattle. Previously developed physiological methodology was felt to be too invasive in this patient population (Charbonneau et al, 1983; Yonemaru et al, 1993). Ideally, the objective outcome measure would be minimally invasive, low cost and easily conducted in the Hospice environment by nursing staff. Discussion with medical staff in a local Hospice resulted in a postulated mechanism of measuring a 'rattle index'. The proposed index involved counting the number of audible wheezes or rattles heard with the aid of a stethoscope placed on the trachea of the patient. Dividing this number by a unit time would produce a 'rattle index'. It was hypothesised that therapeutic success of reducing death rattle would be reflected by a reduction in the 'rattle index'. This method was included on the original application to the Multi-Centre Research Ethics Committee (MREC) associated with the present study (Appendix A). Outcomes of MREC submissions together with other ethical issues will be discussed in more detail in Section 4.4.2.

Before piloting this system, personal communication was made with Back, (2000) who, whilst working in the same field in Cardiff had used a noise meter to provide objectivity in his study. At that time this work had not been published (Back,2000; Back and Jenkins, 2000) however some findings from this work were subsequently published (Back et al, 2001). During the personal communication, Back (2000) also described a method of recording the 'rattle noise' made by the patient using a portable cassette recorder in order to determine whether the sound wave form might indicate pathogenesis of the rattle. Back also utilised wave spectral analysis methods (Yonemaru et al, 1993; Mori et al 1980) on a sample of recordings, with the aim of identifying a difference between patients who responded to anticholinergic treatment and those who did not. In addition Back (2000) also sought to determine the degree of distress felt by relatives via questionnaire, shortly after the patient's death.

Following this communication, a revised methodology was re-submitted to the Ethics Committee (MREC) substituting objective noise monitoring using a noise meter rather than the rattle index, as this was considered to be less invasive for the patient and their family.

The present study did not require or seek to establish breath sound wave forms with a view to detailed analysis. Discussion with an experienced sound engineer (Hillman, 2000) confirmed that a digital sound recording of breath sound could be characterised to give an objective noise level which could act as an outcome measure of clinical efficacy and thus form part of the validation of any subjective noise score used.

Using a Compact Disc (CD) minidisc recorder, chosen for its ease of use, unobtrusive size and portability, two recording microphones were piloted in healthy volunteers. The sound recording was assessed for audible quality and ease of use. The first microphone, approximately 1cm x 1cm, was clipped onto the clothing of a healthy volunteer, approximately 15cm below the subject's mouth and connected to the minidisc recorder via a thin wire. The second microphone was approximately 30cm long and although not attached to the patient, required positioning towards the volunteers mouth at 90 degrees. Photographs were taken to illustrate the appearance of the two microphones in situ, should this have been required to support the Ethics Committee (MREC) submission. In the opinion of the author, the smaller microphone, although requiring attachment to the patients clothing appeared less obtrusive than the larger microphone held away from the patient. A final re-submission to the Ethics Committee (MREC) was subsequently made including an amendment proposing the use of a minidisc recorder with a microphone as an alternative to a noise-meter.

4.4 Ethical Approval

4.4.1 Approval from Hospice Consultants and Medical Directors

During the development phase of the present study, an outline of the proposed methodology was presented at a regular meeting of the West Midlands Palliative Care Physicians with the objective of gaining their approval and support. The meeting was attended by Consultants in Palliative Care, many of whom were medical directors of West Midlands Hospices. At this point in the methodology development, it was proposed that any change in 'rattle noise' which might be attributable to therapeutic intervention would be recorded subjectively by nursing staff attending the patient, and objectively by using a small portable minidisc recorder, with a small microphone attached to the patient's clothing. A recording of a sample of 'rattle noise' would then be analysed digitally. Verbal support and agreement, in principal, for the study to proceed, was given by all Consultants present at this meeting.

4.4.2 Submission to the Multi-Centre Research Ethics Committee (MREC), and Local Research Ethics Committees (LREC)

It was originally intended that this study would be conducted in more than three centres in the West Midlands, it was therefore necessary first to submit project proposals to the Multi-Centre Research Ethics Committee (MREC). As the methodology development for the present study progressed, ethical considerations were raised on behalf of both patients and healthcare staff which became progressively more challenging. The first submission to the MREC was made in December 1999 .

A response from the MREC was received in March 2000 deferring their decision and seeking clarification of some issues. Initial study methodology had proposed the development of a validated 'rattle index'. This would have involved placing a stethoscope over the patient's trachea in order to hear and count the number of breath sounds.

The MREC response suggested that: *in those areas, where monitoring is required, as the death rattle is relatively loud, it could be discreetly monitored by a nurse without placing a stethoscope on the patient. This would cause less disturbance for the patient.*

MREC were not clear about the consent issues in this response. The response was as follows:

'It was felt that the additional burden to the patient was minimal and that consent may not be necessary. The final decision on this aspect has been deferred for further consideration.'

The committee did feel that consent would be needed from the relatives or carers prior to the relative or carer interview, but again sought clarification from an independent reviewer.

In response to these comments, an amendment was submitted to the MREC proposing two alternatives: firstly the use of a noise meter and subsequently a request to use a minidisc recorder which would allow the noise quality to be digitally analysed. The MREC did not object to the use of an instrument that was not in contact with the patient, (noise meter, or minidisc recorder). In order to obtain the best quality recording with the minidisc recorder, and to be least obtrusive to the patient, it was considered that a small microphone, clipped to the patients clothing would be preferable to a larger microphone, held towards the patients mouth. The MREC response in May 2000 required patient consent if a microphone was going to be clipped to the patient. The MREC later however withdrew approval for clipping a microphone onto the patient's clothing (response received August 2000). The proposed use of a minidisc recorder for objective monitoring of the sound level of the rattle noise, had therefore to be abandoned in favour of a digital noise meter, read manually by nursing staff. The alternative recording via the microphone system was considered by the MREC and nursing staff to be too obtrusive(Section 6.2.3).

Following the final approval in October 2000 from the MREC, study details were required to be submitted to Local Research Ethics Committees (LRECs) in the areas covering the participating Hospices. It was decided, in view of the documentation required by different LRECs to submit to two hospice areas

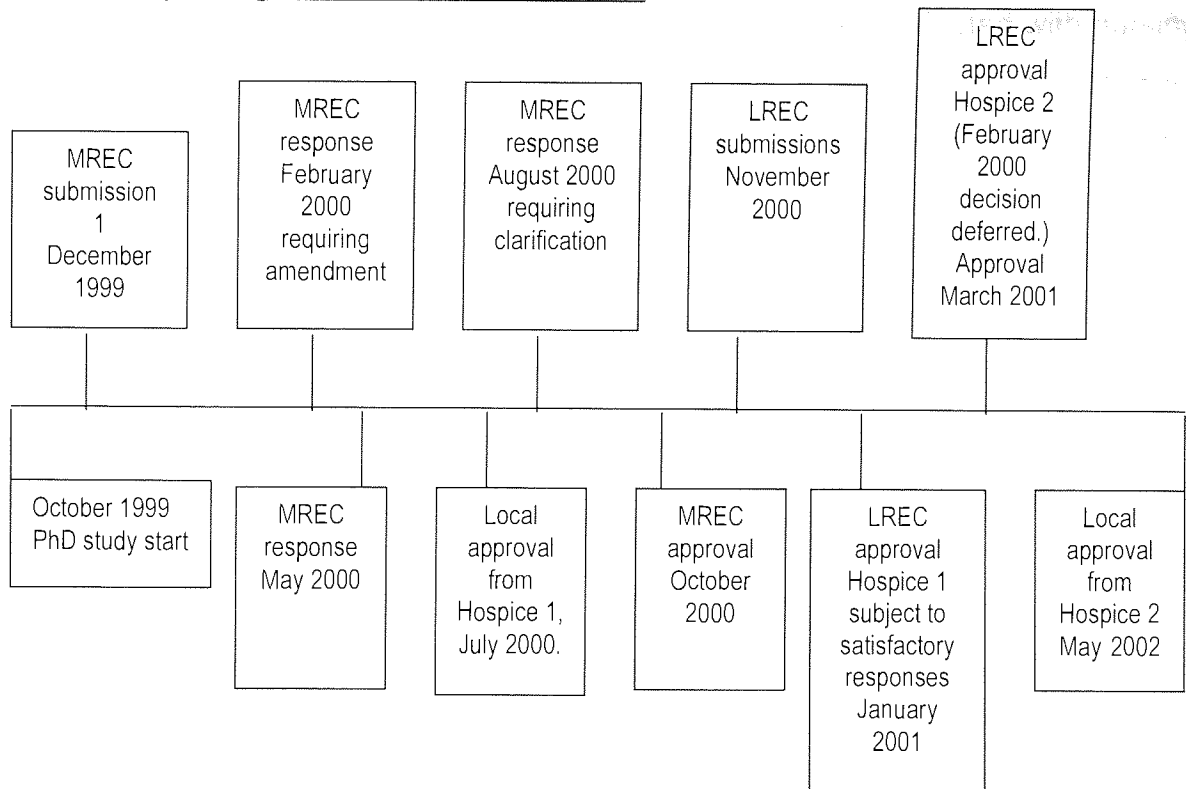
initially, and establish data collection in those areas, before submitting to LRECs further across the West Midlands Region (Appendix A). The submission from the first LREC was confirmed as received in November 2000 and approval given in January 2001 subject to minor clarification. The second LREC confirmed receipt of the application in March 2001 and approval was given later that month.

In addition to the LREC permission, approval also had to be sought from each Hospice. At Hospice 1, which at that time, did not have a fully developed research approval procedure, permission to carry out the study was sought by letter, including copies of the study protocol. A written letter of approval for the study to commence was received (Appendix A). Hospice 2 had an established research and ethics committee and submission required multiple copies of the protocol together with personal representation at a formal meeting.

In 2002, an amendment to the methodology was considered in view of the low number of relatives or carers recruited for interview (Section 8.4). Focus groups of bereaved relatives were considered as an option. The MREC responded that this would require a new research submission. Mindful of the time involved in another ethics submission, at this point in the project it was felt that this could form part of a possible future project.

Whilst the importance of the ethical considerations in this study should not be overstated, every effort was made to explore the area in a sensitive and rigorous manner. The progress and momentum of the study was however significantly inhibited by requirements for re-submission of methodology and subsequent delays before Ethics Committee responses were received. Almost twelve months elapsed between the first submission and final approval from the MREC (Figure 4.4.2).

Figure 4.4.2 Time line showing the progress of the submission for ethical approval for this study through the Ethics Committees.



4.4.3 Nursing ethical issues

Whilst awaiting the decision of the MREC, structured focus group discussions were conducted with groups of nurses from Hospice 1 and Hospice 2 with the aim of informing them about the proposed study and obtaining feedback. Of particular interest were their views on nurse participation by way of recruiting and monitoring patients in the study (Hirsch et al, 2001). Several focus group meetings were held in August 2000 with small groups of day and night nursing and medical staff from Hospice 1 and Hospice 2. The comments and questions resulting from these meetings are shown in Chapter 6 together with feedback from personal representation at the Hospice 2 Research and Ethics committee meeting.

4.4.4 Patient consent procedure

Both the optimum timing and the identification of the appropriate personnel to obtain consent were debated during the group discussions conducted with nursing and medical staff described in section 4.4.3 . As current practice treatment decisions would not be affected by this study, initially the MREC had not insisted on written consent as the study was observational. It was also considered that some patients would not be in a position to give consent, depending on their condition at time of admission to the Hospice. As a result of the group discussions conducted with multi-professional groups in the two hospices (Section 6.2.4) it was decided that consent would be obtained by the admitting doctor, with the patient at the time of admission to the hospice. Consent would be sought from all patients admitted to the hospice unless the admitting doctors felt it inappropriate. Where this occurred, reasons would be noted and accounted for with respect to the total number of subjects recruited. Relatives or carers taking part in the relative or carer interview would be consented by CH or an identified member of the Hospice team who would be conducting the questionnaire. Consent was to be taken by medical staff, CH or by another person if sufficiently trained in taking consent. An information leaflet was designed for patients and carers and approved by the MREC (Appendix B). All doctors at the participating hospices were briefed about the study, including the consent procedure and encouraged to approach patients for consent into the study, both at the beginning of the study and at points of rotational staff change over.

4.5 Development of subjective noise scoring charts

4.5.1 Introduction

The daily decision on when and whether to administer anticholinergic drugs to patients for the treatment of noisy breathing was usually made subjectively. Documentation of the initiation of treatment for death rattle in the patients medical records was inconsistent. In order to capture this subjective data, it was therefore necessary to design and pilot a suitable data collection form.

4.5.2 Design and pilot of subjective data collection forms

A user-friendly graphical noise recording proforma was designed and piloted based on previously reported verbal rating scales of 'rattle' noise (Back and Jenkins, 2000; Hughes et al, 2000) in the Hospice environment. The form (Appendix C) was designed to allow nurses to record any therapeutic interventions given for 'noisy breathing' and subsequent patient response according to the protocol. Data required included: relevant patient information pertinent to the development of 'death rattle', a subjective noise score by nursing staff caring for the patient both at a baseline level and after therapeutic intervention and any adverse effects observed in the patient which may be attributable to the intervention.

Forms were piloted by nursing staff on two patients at Hospice 1. Nurses were asked to use the form to monitor any patients receiving anticholinergics for 'death rattle'. Feedback indicated that the immediate environment in which the patient was being nursed may affect the subjective scoring. One patient had been moved from a four-bedded ward, where the 'death rattle' was audible and considered to be disturbing to other patients. On moving the patient to a single bedded room, the sound was not considered to be a problem. This was the only comment received. No other adverse comments were received and the form was considered to be suitable for the study. Six copies of the form were also left at Hospice 2 for piloting with identified nurses who had volunteered to assist with the study. Despite numerous telephone calls to monitor progress, staff shortages resulted in lack of time for completing forms.

4.6 Validation of noise meter

4.6.1 Introduction

In addition to using a subjective monitoring form to record outcomes, it was considered desirable to employ an objective method of measuring the sound impact of death rattle before and after drug treatment . A decrease in the sound level representing a positive outcome measure for an effect of the treatment intervention.

Several events during the development of the methodology resulted in modifications to the intended method of objective sound recording: Firstly the response from the MREC to not allow a microphone to be attached to any part of the patients' clothing, secondly nursing staff expressed general unease at the proposal to record patients breath sounds. Nurses were also reluctant to ask patient's or relative's permission to record noisy breathing. The noise meter was therefore chosen as the most appropriate method of providing an objective outcome measure.

A simple digital noise meter (AZ 8928 Digital sound meter) was used, which would provide accurate readings for the frequency range of sound from death rattle and would be easy to operate allowing instruction to be give to nursing staff to ensure consistency between operators and centres.

4.6.2 Aim of noise meter validation

To validate the use of a noise meter in order to evaluate noisy breathing using a recorded noise source to determine the most appropriate monitoring procedure for providing objective outcome measures in addition to the subjective nurse noise scoring outcome.

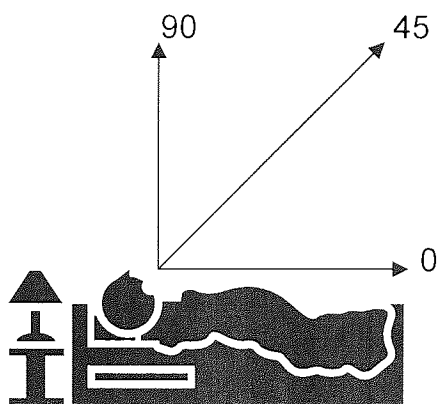
4.6.3 Objectives of noise meter validation

To validate the distance and direction at which the noise meter should be held to produce reproducible and reliable quantitative analysis of death rattle or breath sound noise.

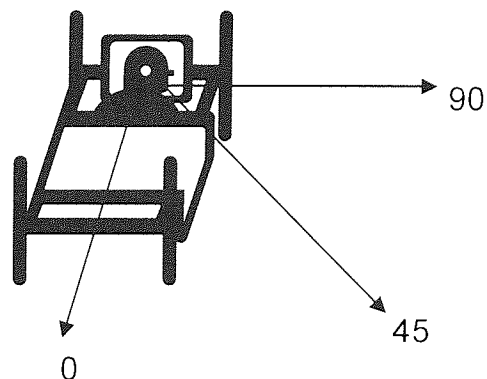
4.6.4 Methodology of noise meter validation

1. A recording was made of normal breathing sounds as a baseline reading. This sound was recorded using a Sony Casette-corder TCM-465V on a new Memorex Chrome C90 tape.
2. A second recording was made onto the same tape under the same conditions of sound similar to that of 'death rattle'. The sound was mimicked by a healthcare professional experienced in palliative care, and considered to be of a sound quality that would prompt prescribing of anticholinergics in a therapeutic setting.
3. The volume setting for play back of the breath sounds and the death rattle were left unchanged throughout the validation. Battery levels were maintained.
4. The Noise Meter was an AZ sound level meter model 8926 Digital Sound Meter set to A weighting, slow response, automatic range. Batteries were new at the time of the validation.
5. The sound source was positioned on the pillow of a bed in a quiet room. The recording was then set to play at a constant volume. Five readings were taken with the Noise Meter for each of the ten predetermined distances from the noise source. Measurements were taken by two operators using a wooden struts fixed at set angles with distances marked on the strut indicating measurement points.
6. Readings were repeated at seven different axes as shown in figure 4.6.4.1 and Table 4.6.4.1 for the rattle noise sound and in two axes for the breath sound (Axes 2 and 3).

Figure 4.6.4.1 Diagram showing angles of measurement from noise source in two planes.



A. Side view



B. Top view

Table 4.6.4.1 The seven axes of measurement from the noise source where noise meter readings were taken at increasing distances of 10 cm from the noise source (10cm to 100cm).

Set-up (axis number)	Side View A (degrees)	Top view B (degrees)
1	0	0
2	0	45
3	0	90
4	45	0
5	45	45
6	45	90
7	90	90

7. The sound level was measured for the first three breaths recorded for baseline and rattle noise level. The highest noise level reading taken was recorded for each recording of three breaths. This was repeated five times at each set distance from the noise source

The validation was conducted in a quiet room with no detectable background noise.

4.7 Patient recruitment

The estimated numbers of patients who would be eligible for the study were based on data collected by the author for a previous audit on subcutaneous drug therapy at several palliative care centres around the West Midlands (Hirsch, 1998). Together with the estimated percentage incidence of death rattle from the available literature and the number of patients treated as hospice in-patients per year, a sample size of 250 patients (one set of records for each patient entered into the study) was calculated to be required in order to detect a statistically significant difference in the outcome of two different treatments at the 5% level (Li Wan Po, 1998). This was considered to be achievable with access to the Hospice centres in the West Midlands Region.

4.8 Patient monitoring

Care was taken to discuss the study methodology with nursing staff at each stage of the present study development. Meetings were held at Hospice 1 and Hospice 2 prior to recruiting patients into the study in order to inform the nursing staff and elicit their support for monitoring patients. At one of these meetings no nurses were able to attend owing to high workload. It was not thought that night staff would be likely to be able to attend due to staffing levels. Regular meetings were carried out at Hospice 1 and Hospice 2 during the study to maintain the profile of the study and encourage patient recruitment. Posters with study details and contact details of CH were posted in clinical staff areas. Folders containing the study protocol together with all necessary documentation and simple instructions on how to use the noise meter were placed in the ward offices (Appendix D). Nursing staff were trained in the use of the noise meter and monitoring procedure. Each time a patient was recruited, where possible, the procedure for monitoring was clarified with nurses present on the shift by CH.

At Hospice 1, CH was routinely present at weekly multidisciplinary ward round review meetings (Mondays), attending the consultant ward round which reviewed all in-patients. It was possible to identify patients who might be recruited into this study at this point and discuss consent of the patient with medical staff. As the part-time clinical pharmacist for the hospice, CH liaised regularly with hospice medical and nursing staff by telephone when not on the hospice site, in order to monitor both the progress of recruited patients and the status of patients who could potentially be recruited for the study. Patient recruitment for the present study started first at Hospice 1 in March 2002.

At Hospice 2 CH attended both a nursing handover meeting on each week (Tuesday) plus a multidisciplinary meeting on Friday morning. As a visiting pharmacist it was felt necessary to spend extra time at the hospice to encourage recruitment. However it became apparent that attendance at the nurse shift was not the most efficient use of time in terms of recruiting patients, although this did allow some opportunity for feedback with regard to monitoring and contribute towards continuing nurse involvement with the study. Patient recruitment began at Hospice 2 in November 2002. Again study briefing sessions took place on the ward for both day and night staff. The study file including all study material was kept in the Ward Sister's office with the noise meter.

Once patient recruitment had begun in Hospice 1 and Hospice 2, the medical director and director of nursing were approached at a third hospice in the West Midlands Region with a view to including this centre in the study. Following their agreement in principle to participate in the study, a series of meetings was scheduled with nursing staff at the hospice and a further request for ethical approval was submitted to the relevant Local Research Ethics Committee. Attendance of the nurses at the scheduled meetings was so poor, that in view of the time required to set up the study, train staff and maintain study momentum it was decided that recruitment of a third centre was not a viable option without further resource.

4.9 Evaluation of relative or carer perspective on distress caused by death rattle and effectiveness of drug treatment

4.9.1 Introduction

Healthcare professionals working in palliative care often maintain that patients are given treatment for noisy secretions primarily for the relief of relatives' distress, although no prospective study had addressed this directly (Watson et al, 2005). The noise described as 'death rattle' is generally believed to cause little distress to the patient unless secretions are directly inhibiting breathing. Although some studies have included nurse scoring of relative's distress (Back & Jenkins, 1997; Hughes et al, 2000,) no published work had yet reported the views of relatives or carers directly about this symptom and its treatment. In order to gain more insight into the view of relatives and carers, the study methodology incorporated a short structured interview, to be carried out on a face-to-face basis with a relative or carer. The interview would be conducted at the time that anticholinergic drugs were being administered to the patient. The interview questions were designed to determine whether relatives or carers were distressed by the noise and whether they were able to quantify this.

4.9.2 Methodology of face to face interviews with relatives or carers.

The outline interview comprised six questions in total. The first four closed questions asked relatives or carers to rate the perceived level of distress caused by the 'death rattle' firstly to the patient and secondly to themselves. The fifth closed question sought the carer or relatives view on the success of the drug treatment of this symptom. The last question was of an open style to allow carers or relatives to express any other feelings related to the noisy breathing or its treatment. The outline for the carer or relative interview is included in Appendix E. Consent was sought from all participants using forms identical to those used for patient consent (Appendix B).

Because of the sensitive nature of the interview, piloting of questions was carried out among nursing staff and bereavement counsellors with respect to appropriate

wording of questions. Choice of interviewer was also felt to be of paramount importance and nursing staff generally indicated that their caring relationship might be compromised if they were asked to conduct interviews for the present study. In Hospice 1, it was decided that the Hospice Medical Director and CH would conduct these sensitive interviews. Bereavement counsellors were kept informed of interview participants with a view to providing support for issues which may be raised in the future as a result of the study. Responses were recorded verbatim using long-hand notes made during or shortly after the interview using the structured questionnaire form. Interviews were conducted in a quiet environment in the hospice chosen by the interviewee. Plans were to use Nudist NVIVO software to assist in the qualitative analysis of data from these interviews.

4.10 Evaluation of healthcare professionals perspective of distress caused by death rattle and the effectiveness of anticholinergic drug treatment using focus groups

4.10.1 Healthcare professionals and prescribing decisions

Anticholinergic treatment for retained secretions causing death rattle, as previously discussed, is often justified by the 'prescriber' to be mainly for the benefit of the carer or relative (Watts et al, 1997). Within the caring environment, different members of the healthcare team are responsible for providing immediate care for a patient and their family. This includes different grades of nursing staff, changing each shift, and possibly different medical staff. Care may be delivered within the patients home, in the hospice or hospital environment. The decision to treat a patient with anticholinergics to reduce death rattle may be influenced by many factors. This may include, perceived distress of the patient, apparent distress of accompanying relatives, or other factors arising from the general care environment, perhaps the ward situation or proximity of other patients. Focus groups were chosen as a method of exploring the perspectives of healthcare professionals engaged in the palliative care of patients, with regard to distress caused by death rattle and their perceptions of the effectiveness of current treatments.

4.10.2 Preparation for the focus groups.

It was intended to conduct focus group sizes of 8-10 participants based in Hospices around the Region, to include a range of staff grades, responsibilities and experience. Planning and conduction of the focus groups was carried out according to procedures suggested by Morgan (1998) and Bloor and co-workers (2001). Letters were circulated to the Hospices concerned to establish the most convenient time to run such sessions. Agreement was given for the focus groups to be conducted during the working shift, as no external funding was available, and taking into consideration current staffing in most institutions, it was thought that staff were unlikely to attend a focus group outside their working shift.

Focus groups were conducted using similar groups of staff at the two hospice centres for which Ethics Committee approval had been given. This allowed comparison of the views of ward in-patient staff, home-care teams and Specialist Registrar medical staff. The ward staff groups would normally contain a mixture of grades of nursing staff whereas the home care team was restricted to more experienced nurses. The Specialist Registrar doctor's focus group of included doctors at different stages of their specialist registrar training, who rotated around the hospices within the West Midlands Region. Although it would have been desirable to conduct focus groups in other hospice units, the level of interest and support from one of the other hospice centres specifically approached was not considered to be sufficient to produce worthwhile results.

For hospice nursing staff working on the in-patient units, personally addressed letters were sent to each of the staff available at the time agreed with the ward sister on duty, giving the background to the study and inviting them to attend the session (Appendix F). Personal verbal reminders were also given. Later, because of poor response to this method of recruitment, and due to frequent changes in the anticipated personnel on that particular shift, a general letter of invitation to attend the focus group was issued to the ward sister for distribution together with details of the study background.

For the nursing staff working in the Hospice 1 home care team, a time for the meeting was scheduled for one afternoon and all of the team invited. For the Hospice 2 home care team and the Specialist Registrar's focus group, a special 'protected meeting time' was made available. An open invitation was extended to all those attending the meeting to take part in the focus group.

4.10.3 Conduct of the focus groups

A format for introduction and asking questions was devised to ensure consistency at the start of each group. A set of 'flash' cards were used with each group, set out on the table in random order as prompts to stimulate discussion around the topic.

Focus groups were all held in booked rooms on the hospice premises, apart from the registrar group which was held in a teaching room on a hospital site central to the West Midlands Region. The rooms were chosen to be quiet and undisturbed but to remain easily accessible for staff. Light refreshments were provided but there was no remuneration for participants. It was ensured that each participant had read and understood the purpose of the study and the focus group and each participant signed a consent form (Appendix F).

It was planned that each focus group discussion would not last more than 1 hour. Two tape recorders (a dictation machine and small portable tape recorder using CD60 tape) were used for each session, one at either end of a table placed centrally within the group. CH facilitated each group. There was no observer for any group. A short summing up was carried out at the end of each group and group members were reminded about the confidentiality issues before beginning the group discussion and at the end of the session.

The resulting tape recordings from each group were transcribed verbatim by CH to produce the focus group transcripts. Each tape was then listened to twice more whilst reading the transcripts, once immediately after the first transcription to identify any errors, the transcription was then read together with the tape recording to check for accuracy again, prior to coding. Other manual notes were made by CH immediately after the focus groups regarding any issues that had occurred during the meeting, which might not be obvious on the sound tape.

Axial coding took place against a plan of the themes that had originally been defined by the cards at the initiation of the group and repeatedly emerging themes from the focus group discussions (Krueger, 1998). Coding and analysis was carried out using N. VIVQSR Nvivo (July 2005) software.

5 Results of the systematic review of the literature focussing on studies of the treatment of death rattle with anticholinergic agents.

5.1 Overview of studies retrieved

In line with the process advocated by the Cochrane review process (Green and Higgins, 2005) an attempt was made to critically appraise the previous studies on the treatment of death rattle in palliative care patients.

Thirteen published papers were accessed and compared for reliability, validity and relevance to the treatment of death rattle with anticholinergic agents. Each paper was critically appraised in order to assess recruitment methods, exposure measurement, outcome measurement, and identification of confounding factors (Table 5.1.1). Details of the results from these studies are then shown in Table 5.1.2. Some unpublished work was accessed (Back, 2000; Back and Jenkins, 2000) parts of which were subsequently published. Published details are included in the appraisal table. The papers are arranged in the table in chronological order of publication.

Only one published randomised double-blind study was found, in which patients were randomised to receive either scopolamine (hyoscine hydrobromide) or placebo (Likar et al, 2002). One paper published since the start of this study, documented the intent to conduct a controlled trial of two antimuscarinic drugs in the management of noisy respirations associated with death rattle (Rees and Hardy, 2003). The publication relating to this trial focused on the consent procedure only and no results relating to treatment effects had been published at the time of writing this thesis.

The remaining studies could be described as observational case series, generally without controls, designed to allow a greater understanding of the symptom commonly given the name 'death rattle', and to detect factors which might predispose patients to developing death rattle. Some studies also sought to determine the treatment administered in order to control death rattle. Assessment

of the effectiveness of drug and non-drug treatments of death rattle occurred within some of these studies. One study audited outcome of three different treatment protocols against a standard outcome (Hughes et al, 2000)

The titles of the studies were similar in theme over time. The most recent paper (Morita et al, 2004) was still seeking to determine aetiologies and incidence of death rattle in cancer patients, as did six of the previous studies.

As most of the studies retrieved for appraisal were not randomised controlled trials, regarded as the most appropriate way to address questions regarding therapeutic efficacy, attempts were made to critically appraise the literature according to criteria shown in Tables 5.1.1 and 5.1.2 .

Table 5.1.1 Appraisal details for the systematic review of thirteen studies looking at anticholinergic treatment for death rattle in palliative care

palliative care

Authors	Title of Paper	Primary outcome	Entry criteria	Endpoints	Statistical tests	Number of centres	Retrospective/ Prospective	Randomised, controlled study Yes/No
Lichter and Hunt, (1990)	The last 48 hours of life.	Observational record of symptoms during the last 48 hours of life.	200 consecutive patients on the hospice program	Overall incidence of symptoms, including noisy breathing. An assessment of frequency of use and the effectiveness of HHBr was given.	None reported	One (New Zealand)	Prospective	No
Power and Kearney, (1992)	Management of the final 24 hours.	Assessment of the medication given in the final 24 hours of life.	100 consecutive patient deaths in the Hospice.	List of medication and symptoms during the final 24 hours of life from medication chart review.	None reported	One (Ireland)	Retrospective	No
Lucas et al, (1994)	Abstract: The use of GLY by syringe driver to alleviate bronchial secretions.	To establish whether GLY might be a suitable alternative to HHBr.	Not specified	Not stated	None reported	One (UK)	Prospective	No

Authors	Title of Paper	Primary outcome	Entry criteria	Endpoints	Statistical tests	Number of centres	Retrospective/ Prospective	Randomised, controlled study Yes/No
Ellershaw et al, (1995)	Dehydration and the Dying Patient	Assessment of the relationship between the level of patient hydration and respiratory secretions, thirst, dry mouth, and biochemistry.	Patients admitted to a hospice, (entered into study when no longer taking oral medication).	<ol style="list-style-type: none"> No. of subjects developing respiratory tract sounds (RTS) if audible, or HHBr given for RTS. Infection No. of subjects with persistent RTS despite treatment with HHBr. No. of days from initial assessment till death. No. of subjects requiring suction for RTS. Blood tested for markers of hydration. 	Mann- Whitney U-test and Chi-square test.	One (UK)	Prospective	No
Bennett, (1996)	Death Rattle: An audit of hyoscine (scopolamine) use and review of management.	Establishment of patterns and determinants of HHBr usage in treatment of death rattle.	100 consecutive deaths over 5 months. (Review of patient medical records and drug administration charts)	<p>Presence of hepatic or cerebral disease; non-malignant disease; cardiac disease; COPD; LVF; regular use of diuretics; MND/MS.</p> <p>Administration of injections HHBr from medical records and drug administration charts during the final 48 hours before death as 2x 12hour, and last 2 x 6hr periods plus medication given in the last 48 hours before death.</p>	Chi-square test with Yates' correction. Fisher's exact test and Spearman's correlation coefficient.	One (UK)	Retrospective	No

Authors	Title of Paper	Primary outcome	Entry criteria	Endpoints	Statistical tests	Number of centres	Retrospective/ Prospective	Randomised, controlled study Yes/No
Back and Jenkins, (1997)	Abstract : A study of 'death-rattle' in terminal care.	To define the natural history of 'death-rattle' and collect baseline data on this and its management. To pilot a measurement tool to assess efficacy of treatment.	Patients admitted to in-patient units over 12 months	Categorical rating scale used to record amplitude of death rattle, 30 minutes after injection of HBr and 4-hourly thereafter. Carer distress was rated by nursing staff using a categorical scale. Details of drug administration were recorded.	Not described	Two specialist palliative care units (UK)	Prospective	No
Hughes et al, (2000)	Audit of three antimuscarinic drugs for managing retained secretions	Audit of three guidelines, reflecting 'traditional' use of HBr, GLY, HBr. Standard: That secretions should be relieved in 50% of patients and distress in at least 90% of relatives.	Consecutive patients near death with persistent noisy secretions despite repositioning. HBr and HBr given to all patients at first hospice. GLY given at both hospices. Convenience sample of 37 patients in each audit.	Intensity of noise due to secretions, and relatives distress measured by subjective scoring system.	Not described	Two specialist palliative care units. (UK)	Prospective	No

Authors	Title of Paper	Primary outcome	Entry criteria	Endpoints	Statistical tests	Number of centres	Retrospective/ Prospective	Randomised, controlled study Yes/No
Morita et al, (2000)	Risk factors for death rattle in terminally ill cancer patients: a prospective exploratory study.	Identify risk factors for developing death rattle.	All cancer patients admitted consecutively to a specialist palliative care unit Sept 1996 – Oct 1998.	All patient details plus presence or absence of death rattle were recorded daily until death. Presence or absence of death rattle, 12 and 24 hours after initial assessment, and few hours before death.	Multiple logistic regression analysis in a forward stepwise fashion using presence of the symptom as the independent variable & patient characteristics & tumour location, as risk factors by univariate analyses as the dependant variables.	1 specialist palliative care unit. (Japan)	Prospective.	No
Back et al, (2001)	A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle.	Assess change in response of symptomatic treatment with HBr (phase 1) and GLY (phase 2). To establish comparative efficacy. And cost effectiveness.	Each dying patient who developed death rattle during the study periods. Phase 1, 11 months, Phase 2, 9 months.	Subjective noise scores at 30 minutes, 1 hour and final score before death. Drug administration chart analysis Drug Costing. Drug usage compared	Chi-square test.	One (UK)	Prospective	No

Authors	Title of Paper	Primary outcome	Entry criteria	Endpoints	Statistical tests	Number of centres	Retrospective/ Prospective	Randomised, controlled study Yes/No
Likar et al, (2002)	A controlled randomised double-blind study comparing the effectiveness of scopolamine hydrobromide with placebo in patients with death rattling.	Efficacy of treatment with HHBr 0.5mg vs saline(placebo) given at 0, 4 and 8 hours, for the treatment of death rattle and assessed every 2 hours for 12 hours.	Patients admitted for terminal care to a hospital who were unconscious, with a life expectancy of less than 3 days and increased mucus formation with loss of swallowing and cough reflex.	Mean score of death rattle was assessed on rating scale of 1-5 every two hours for 10 hours, plus restlessness and pain on a scale of 1-3.	Chi-square test to determine differences in mean death rattle scores. Mann-Whitney U-test for side effects.	One	Prospective	Yes
Wildiers and Menten, (2002)	Death rattle. Prevalence prevention and treatment.	Occurrence and incidence of death rattle in consecutive patients as recorded in case notes	Patients admitted to palliative care unit consecutively over 9 months.	Proportion of patients noted to have death rattle. Proportion of patients receiving anti-secretory treatment. Effectiveness of the treatment defined as 'no evidence for persisting disturbing rattle'. Background information on pathology, age gender, time of anticholinergic administration and side effects recorded.	Not described	One (Belgium)	Retrospective	No

Authors	Title of Paper	Primary outcome	Entry criteria	Endpoints	Statistical tests	Number of centres	Retrospective/ Prospective	Randomised, controlled study Yes/No
Kass and Ellershaw, (2003)	Respiratory tract secretions in the dying patient: A retrospective study.	Incidence, onset time and risk factors, for developing respiratory tract secretions.	Patients dying in the hospice over 12 months, and entered into the Liverpool Care Pathway for the care of the dying patient. Patients who had at least one episode of RTS. If only one episode – not considered.	RTS presence or absence recorded at 4-hourly intervals. Response times measured as time to first response and time to permanent response. Response time for permanent response, defined as 'time from first RTS until symptoms permanently absent until death'.	Chi-Square test. Simple linear regression for age and time on Liverpool Care Pathway	One(UK)	Retrospective	No
Morita et al, (2004)	Incidence and underlying etiologies of bronchial secretions in cancer patients: a multicentre, prospective observational study	Observational to investigate the association between hydration status and symptoms.	Consecutive terminally ill cancer patients from multiple centres. Detailed exclusion criteria: prior communication difficulty; liver cirrhosis; renal failure; and other medical complications that could influence fluid retention.	Bronchial secretions with severity grade. Peripheral oedema and Pleural effusion also graded.	Multiple logistic regression analyses. Univariate analyses with Mann- Whitney U-test and Chi-square test (Fisher's exact test).	Multi-center 14 oncology units, 19 Palliative care units, 4 home based (Japan.)	Prospective	No

Key: Hyoscine hydrobromide – HBr Glycopyrronium bromide- GLY Hyoscine butylbromide – HBBr RTS – respiratory tract sounds
 COPD- Chronic obstructive pulmonary disease LVF – Left ventricular failure MND- Motor Neurone disease MS – Multiple sclerosis

Table 5.1.2 Summary of findings from the studies (detailed in table 5.1.1) included in the systematic review including whether ethical approval and consent was obtained, definitions of death rattle used and whether presence of underlying infection was recorded.

Authors	Report contained reference to ethical issues or consent	Definition of respiratory tract symptoms.	Presence of possible respiratory tract infection (RTI) recorded	Summary of results
Lichter and Hunt, (1990)	None recorded	'Moist respiration and the Death Rattle' (not defined)	Not noted	Noisy and moist breathing was recorded in 56% of patients. Noisy respiration requiring medication noted in 25% of patients. HHBr noted to have immediate effect in 94% of patients, 6% requiring repeated doses. 31% of patients needed only nursing intervention. Overall 91.5% of patients were described as dying peacefully.
Power and Kearney, (1992)	None recorded	No definition. (interpretation of notes)	Not noted	Evidence was found from patients medical records of excess respiratory secretions plus pain and agitation. 44/100 patient's charts recorded respiratory secretions, in 9 patients this was noted as particularly severe. 70/100 patients were recorded to have had anticholinergic drugs, therefore the incidence of death rattle may be higher than was recorded. Furosemide was also administered to 15 patients with presumed persistent respiratory symptoms and suction performed in 9 patients. 25/57 patients receiving HHBr at time of death had treatment initiated within the final 24 hours of life. Agitation was noted in 6 patients who were changed to HHBr but may have been pyrexial.
Lucas et al, (1994)	None recorded	No definition	No noted	Provisional results reported in abstract. Experience from 11 patients studied over 6 months showed that it seemed suitable to administer GLY via a syringe driver. Treatment seemed more effective if GLY started before accumulation of secretions.
Ellershaw et al, (1995)	Ethics approval patients or relative's consent obtained.	'Sounds audible at the bedside' recorded if: a) RTS audible at time of initial observation. b) HHBr been given in past 12 hours to treat RTS.	Presence of RTI if green or yellow sputum recorded in last 48 hours, or patient prescribed antibiotics.	82 patients were admitted to the hospice during the study with a mean age of 73 (43-89) No subcutaneous fluids were administered. 23% of patients had lung carcinoma, 9% with lung metastases. Six patients met the criteria for infection (7%). Time of study entry until death was 1-5 days 18 patients (22%) did not respond to HHBr, 3 patients were given suction for secretions. In total 92% of subjects developed RTS in terminal phase. 70% patients were controlled with HHBr, 22% had persistent secretions.. Figures suggested some association with hydration status and RTS although this was not statistically significant.

Authors	Report contained reference to ethical issues or consent	Definition of respiratory tract symptoms.	Presence of possible respiratory tract infection (RTI) recorded	Summary of results
Bennett, (1996)	No consent or ethics details recorded.	Not defined	Respiratory infection not included in the risk factors.	96 patients recruited (56:40 F:M) with a mean age of 71 years. Median length of stay was 9 days. 26(27%) patients had HHBr infusion at death. 50% of patients received HHBr injection in the last 48 hours, 45% of patients had HHBr in last 6 hours of life. HHBr was associated with longer duration of stay(> 9 days) & cerebral malignancy. Half of the patients dying in the hospice received HHBr.
Back and Jenkins,(1997) Abstract	None recorded in abstract.	No definition but included a categorical rating scale to record amplitude of noise of death-rattle.	Not noted in abstract	The incidence of death-rattle was 43%. The median interval from entering the study to death was 11 hours, (mean 20 hours, range 10min – 5 days.) The lowest recorded noise score, 1 (audible only very close to the patient) was present in 19% of patients, score 2 (clearly audible at the end of the bed in a quiet room) in 44% of patients, score 3 (clearly audible at 20 feet in a quiet room. 87% of patients had a subcutaneous injection of HHBr, 57% of patients received a subcutaneous infusion of HHBr, 3% of patients had no HHBr. Noise score improved 30 minutes after first dose of HHBr in 58% of patients. Improvement in noise score from first record to death was noted in 52% of patients. A correlation between noise score and nurse rated carer distress level was identified. iet room) in 37% of patients
Hughes et al, (2000)	None recorded.	No definition given, term 'retained secretions' used.	Not recorded	Patients in the three centres represented 44%, 31% and 50% of all inpatient deaths respectively. 35% of patients responded to their first HHBr injection, 54% to their first HHBr injection and 46% to their GLY injection. Of those patients responding to the first HHBr injection, secretions recurred in more patients in a shorter period of time. Fewer patients responded and remained settled with the first 3 doses HHBr (32%) compared to HHBr (38%) and GLY (49%)

Authors	Report contained reference to ethical issues or consent	Definition of respiratory tract symptoms.	Presence of possible respiratory tract infection (RTI) recorded	Summary of results
Morita et al, (2000)	None recorded	'Sound audible at bedside'	Pulmonary oedema or infection noted by crackles on auscultation or X-ray.	<p>294 patients were recruited, 245 died and were analysed (136F:109M), the mean age was 66 years. Median stay was 25 days. Carcinoma of lung was the most common site of carcinoma.</p> <p>107 (44%) patients developed death rattle. 44(41%) patients received HHBr. Additionally hydration was withdrawn from 21% of patients, suction carried out in 12% of patients, sedation given to 4.7% of patients. Death rattle persisted for the initial 24 hours in half of the patients and disappeared in 71% until death.</p> <p>Patients with brain, lung and bone carcinomas were more likely to get death rattle. No association was found in length of stay, age or sex.</p> <p>Persistent death rattle was associated with lung cancer, pulmonary infection or oedema, but not conscious levels or brain involvement.</p> <p>Study limitations acknowledged that the validity of measurement methods to assess pulmonary infection and oedema had not been fully established.</p> <p>No strict treatment protocol was adopted due to ethical considerations. Physician's preference of treatment and use of subcutaneous fluid could have influenced the outcome.</p>
Back et al, (2001)	Only Ethics committee LREC. No mention of consent.	No definition but scoring system had used defined ratings of sound.	Not noted.	<p>In the 30 bedded unit, there were 294 patient deaths during 11 months in phase 1 and 240 deaths in phase 2 (9 months). In phase 1, 129 patients developed RTS (44%) and in phase 2, 75 patients (36%) developed RTS.</p> <p>Data were collected for 128(99%) and 63(84%) in each phase respectively. Distribution of diagnoses were similar in each phase.</p> <p>'Death phase' was 22 hours in phase 1 and 27 hours in phase 2 (range 5 minutes -5 days.)</p> <p>108 patients (84%) received HHBr, 103 patients had noise scores recorded(80%) at 30 minutes (Phase 1).in Phase 2, of 62 patients having GLY, 56 (89%) had noise scores recorded at 30mins.</p> <p>More patients received a second injection of GLY in Phase 2 (50% phase 2, 33% phase 1).When the later 30 minute score was compared with the first, more scores improved in phase 2 (40% vs 27%) compared with 57% vs 56% in phase 1.</p> <p>In phase 1, 46 patients (51%) had an improved final noise score compared to the initial score. In phase 2, 24 patients (42%) had improved final noise scores compared to initial scores after injection. Neither 1 hour noise scores or final noise scores were different between the phases using Chi-square test.</p> <p>More patients in Phase 2 received anticholinergic drugs.</p> <p>Fewer patients had reduced noise scores at 30 minutes with GLY than HHBr. Authors concluded that GLY 0.2mg was less effective than HHBr 0.4mg at 30minutes. Analysis of drug costs was not conclusive due to possible increased need for other drugs when GLY used.</p>

Authors	Report contained reference to ethical issues or consent	Definition of respiratory tract symptoms.	Presence of possible respiratory tract infection (RTI) recorded	Summary of results
Likar et al, (2002)	Ethical approval gained, consent not reported	Defined as 'type 1' death rattle, subjective 1-5 rating scale used.	None	31 patients were recruited, 15 in the treatment group and sixteen in placebo group. Demographics of each group were similar. The study was double blind for the first 8 hours and at 12 hours, if needed the patient was given treatment A (HHBr 0.5mg) or B (saline) 4-hourly until death. If there was no difference in rattle after 24 hours, drug administration was stopped. Between measurements at 6 hours and 8 hours, the 'active group' showed tendency to less death rattle on subjective scoring by trained observers, but frequent reports of agitation and pain was recorded by observers the active group than the placebo group, even though patients were unconscious.
Wildiers and Menten, (2002)	None described	None described	Not directly recorded	107 patients were recruited. 25 (23%) patients developed Death rattle, 9 of these patients had primary lung carcinomas. Palliative sedation was noted to be practiced. Five patients were noted to have intravenous catheters in place, 3 containing saline. 20 of the 25 patients received subcutaneous injection of HHBr 0.25mg. 5 patients received intravenous infusion of HHBr 1-2.5mg. In 12 patients HHBr treatment was given for less than 24hrs, in 19 <48 hrs and in 3 patients for more than 4 days and was not effective. HHBr was found effective in 18 patients. In 6 patients there was persisting rattle and in most, other explanations were present (fever, aspiration, acute respiratory distress). No confusion was documented or other side effects noticed and no patients required catheterisation.

Authors	Report contained reference to ethical issues or consent	Definition of respiratory tract symptoms.	Presence of possible respiratory tract infection (RTI) recorded	Summary of results
Kass and Eilershaw, (2003)	None described.	RTS presence or absence recorded at 4-hourly intervals 'sound audible at bedside'	Not recorded on the electronic database.	(Observed RTS were treated with HHBr stat 400 mcg plus subcutaneous infusion of 1.2mg) 296 patients died in the 30 bedded hospice over 12 months, of these, 202 were entered onto the Liverpool Care Pathway for the dying, having a mean age of 67 years (M:F 0.85:1). 99/202 patients on the Liverpool Care Pathway developed RTS, of these 88 patients had observations recorded. Identified risk factors for developing RTS were Male gender, lung cancer diagnosis, and prolonged dying phase. 59/99 with RTS received HHBr for more than 4 hours 64.4% of these 59 responded and died symptom free. 18 patients (30.5%) responded to HHBr in less than four hours and were symptom free until death. 20 patients (33.9%) died symptom free but response time was more than 4 hours. 21 patients died with RTS, 11 had some response to HHBr, but 10 (16.9%) had no symptom free times. (Response time for permanent response = time from first RTS until symptoms permanently absent until death.)
Morita et al, (2004)	None described	RTS = 'sounds audible at the bedside'. Severity of secretions graded as Back et al, (2001) of grade 1 or greater, medication administered, or suctioning, indicated presence of RTS.	Pneumonia noted as underlying pathology.	310 patients were recruited, (54 from oncology units, 237 from Palliative Care Units and 19 from home-based care). Pneumonia was diagnosed in 22% (69) of patients, and dysphagia in 9% (28) of patients. Artificial hydration was performed in 34% (105) with median of 700ml per day. Bronchial secretions were observed in 41% in the final 3 weeks before death. An association with lung cancer, pneumonia and dysphagia was found with developing RTS. No association was found between developing RTS and oedema or pleural effusion. Between 22 and 10% of all patients required suction 3 or more times a day. Patient distress was described as considerable in 9% of patients having suction. Findings estimated that bronchial secretion developed in about 40% of all dying patients and that symptoms were Grade 3 in 5-7%.

Key: Hyoscine hydrobromide – HHBr Glycopyrronium bromide- GLY Hyoscine butylbromide – HBBr RTS – respiratory tract sounds
 COPD- Chronic obstructive pulmonary disease LVF – Left ventricular failure MND- Motor neurone disease MS – Multiple sclerosis hrs - hours
 RTI – Respiratory tract infection.

5.2 Comment on the study methodologies

Details of the results for each paper were assessed against the criteria shown in Tables 5.1.1 and 5.1.2

5.2.1 Primary outcomes of the studies

Seven studies focused on the prevalence of symptoms including death rattle in the terminal phase of the patient's illness. Only one of these studies also specifically addressed outcome of drug treatment (Back and Jenkins, 2000). This observational case series aimed to determine the incidence of death rattle in the observed populations and identify any risk factors for developing the symptoms. Ellershaw and co-workers (1995) studied whether levels of hydration, as provided by subcutaneous infusion, affected the incidence of respiratory tract secretions, causing death rattle. Six of the studies primarily addressed the use of drug treatment for death rattle and included some assessment of treatment outcome (Lucas et al, 1994; Bennett, 1996; Back and Jenkins, 2000; Hughes et al, 2000; Likar et al, 2002; Back et al, 2001). Drug treatments included glycopyrronium and hyoscine hydrobromide and one paper addressed the use of hyoscine butylbromide (Hughes et al, 2000).

5.2.2 Recruitment details and patient populations

Nine studies were prospective. Entry criteria for the prospective studies followed consecutive patient admissions to the institutions for varying periods of time ranging from 5 to 11 months.

Four studies were retrospective and reviewed patient records. Two of these papers stated that cases were recruited on the basis of deaths which had occurred consecutively (Power and Kearney, 1992; Bennett, 1996), one reviewed data on 202 patients who died within a 12 month period (Kass and Ellershaw, 2003) and one (Wildiers and Menten, 2002) reviewed records of 112 patients admitted to the

hospice in order to identify deaths. The time period over which the deaths had occurred, was variably stated. Extensive exclusion criteria were stated by Morita and co-workers, (2004) whereas none of the other studies stated exclusion criteria.

The only randomised controlled trial to assess outcome of treatment (Likar et al, 2002) recruited 31 patients who were admitted to a federal hospital, not fully conscious with a life expectancy of hours to less than three days. In addition those patients recruited had increased mucus formation in the upper respiratory tract with loss of swallowing and cough reflex, described as terminal rattle 'type 1'. Exclusion criteria include patients who were conscious, those with a life expectancy of more than three days and if patients had been given anticholinergic drugs prior to entry into the study.

Most of the studies were carried out in what appeared to be described as single centre 'palliative care institutions', apart from one (Morita et al, 2004) where multiple centres were used to recruit patients including oncology centres and home based patients. Two studies (Back and Jenkins, 1997; Hughes et al, 2000) used two centres and these centres appeared to be served by the same medical teams.

Countries of origin included, Austria (Likar et al, 2002), Ireland (Power and Kearney, 1992), New Zealand (Lichter and Hunt, 1990), Belgium (Wildiers and Menten, 2002), the remaining nine studies were carried out in the United Kingdom.

None of the studies included power calculations or made statements about the numbers of patients to be included in the study. Only one study included less than 30 patients (Lucas et al, 1994), 11 patients were included in this series, which was reported as a provisional study. Numbers of patients in other studies varied from 31(Likar et al, 2002) to 310 patients (Morita et al, 2004).

5.2.3 Intended endpoints and analytical techniques used.

Table 5.1.2: Summary of 30 patients.

There was variability in the prospective and retrospective studies in terms of the details monitored, the way that they were recorded and in the definitions and terminology. These factors are explored in further depth in the following section.

Statistical tests were described in five of the prospective studies and in two retrospective studies. Kass and Ellershaw (2003) used a Chi-square test to test the significance of any relationship between the development of death rattle and patient gender or underlying pathology and simple linear regression was used to assess the significance of continuous variables of age and time in the dying phase, on the development of death rattle in their retrospective study of 202 patients. Male gender was found to be associated with a higher incidence of developing death rattle, however the authors acknowledged that the database did not account for details of past smoking habits, infection or other underlying pathology apart from the main diagnosis. There were a high proportion of missing observations in the last hours before death which may have introduced bias. Patients were also excluded from this study because they had not received the recommended regimen of hyoscine hydrobromide – patients receiving alternative treatments may have been those who did not respond to the ‘recommended regimen’, again leading to bias in the results (Table 5.1.2). Bennett (1996) used Chi-square tests with Yates’ correction to determine the likelihood of patients receiving bolus injection of hyoscine hydrobromide in addition to infused hyoscine hydrobromide in the 6 hours prior to death. Fisher’s exact test was used to describe to association between a) length of stay and b) the patient having cerebral malignancy. The Yates’ correction and Fisher’s exact test are generally used when the sample sizes are small, although there is no consensus as to whether the Yates’ correction is valuable (Li Wan Po, 1998). Spearman’s rank correlation coefficient was used to demonstrate that there was a tendency that the cumulative dose of hyoscine hydrobromide administered in the final 24 hours was greater in patients with a longer duration of stay and the presence of cerebral metastases. These tests were appropriate for the data being analysed.

Of the statistics reported in the prospective trials, in a study of 85 patients (Ellershaw et al, 1995) the Mann-Whitney U test was used to compare the medians for biochemical values between the two groups, those developing and those not developing death rattle, together with the Chi-square test for comparison of proportions of dehydrated and non-dehydrated patients developing death rattle and reporting other symptoms. Back and co-workers (2001) used the Chi-square test to determine whether there was a difference in noise scores between two different treatment phases (each phase having 294 and 210 patients respectively). Morita and co-workers (2000) used multiple logistic regression analyses to identify risk factors for developing death rattle in a sample of 245 cancer patients who died. In a later study (Morita et al, 2004) similar logistic regression analyses were used to determine that development of death rattle was related to a diagnosis of primary lung cancer, pneumonia and dysphagia in a multi-centre study recruiting 310 patients. The Mann-Whitney U-test and Chi-square test with Fisher's exact test was also used.

The only randomised controlled trial (Likar et al, 2002) employed the Chi-square test to detect differences between the treatment and placebo group with regard to mean death rattle averages. Side effects were analysed using Mann-Whitney U-test. Only 31 patients were recruited in this study however. The death rattle scores were subjective measures of sound (1-5) as assessed by a carer and the validity of using such statistics to assess these measurements in a small population could be questioned. The side effects measured related mainly to pain and agitation observed by carers, in patients who were not fully conscious.

The use of the various statistical tests seemed appropriate with regard to the categories of data being analysed. More questionable, particularly with regard to the assessment of efficacy of treatment would be whether the outcomes measured were a valid representation of the clinical situation.

5.3 Summary of findings from the systematic review varied between

with the purpose of the study

and the nature of the study

5.3.1 Consent and ethical issues within the studies

The requirements for obtaining patient consent and ethical approval for research, audit and surveys have changed over the years and also differ from country to country (Hearnshaw, 2004). Of the studies appraised, three studies reported that ethical approval had been obtained (Ellershaw et al, 1995; Likar et al, 2002; Back et al, 2001). Consent was reported to have been gained from patients or relatives in only one published study (Ellershaw et al, 1995). Further discussion regarding consent and ethical issues will be taken up in section 10.2.

5.3.2 Differences in definitions of outcome measurements and data collection

5.3.2.1 Definitions and measurement of death rattle

Although all of the studies sought to record the incidence of death rattle in the series of dying patients and some studies attempted to record the efficacy of treatment, the definitions of death rattle used and the methods of monitoring treatment efficacy varied.

Various definitions of respiratory symptoms have been used: '*moist respiration*' (Lichter and Hunt, 1990) ; '*the death rattle*', or the term '*respiratory tract sounds*' (RTS), defined as '*sounds audible at the bedside produced by the movement of secretions in the hypopharynx or the bronchial tree in association with respiration*'. This latter definition used initially by Ellershaw and co-workers (1995) was taken up by future authors as 'standard' terminology. Likar and co-workers (2002) described entry criteria for patients in their study as being unconscious, with increased mucus formation in the upper respiratory tract with loss of swallowing and cough reflex, exhibiting 'Type 1' death rattle using the classification described by Bennett (1996).

The measurement of the death rattle phenomenon however varied between studies. In prospective studies death rattle was identified for purposes of the study as 'noisy breathing requiring medication' (Lichter and Hunt, 1990). Ellershaw and co-workers (1995) used the defining symptoms of RTS (respiratory tract sounds) 'audible at the time of initial observation', or 'administration of hyoscine hydrobromide in the past 12 hours' as an indicator of death rattle. The RTS definition was also used by Morita and co-workers, (2000 and 2004). No definition of the symptom was given in the other prospective studies but different categorical rating scales were used (Table 5.1.2). The rating scale used by Back and Jenkins (1997) has been used in subsequent papers (Morita et al, 2004).

Retrospective studies employed a variety of descriptive criteria to establish that death rattle had occurred in a patient such as entries on patient medical records specifically noting presence of 'respiratory secretions', recorded administration of an anticholinergic drug, administration of furosemide where there were 'presumed persistent symptoms' and where laryngeal suction had been performed and recorded.

5.3.2.2 Data collection and measurement of identified contributory factors which might affect the development of death rattle.

A record of the possible presence of respiratory tract infection was specifically used as a criterion in the critical appraisal. This criterion was defined as 'yellow or green sputum noted in the last 48 hours' by Ellershaw and co-workers (1995). Pulmonary oedema or infection was noted on X-Ray or auscultation by Morita and co-workers (2000), peripheral oedema and pleural effusion was noted in addition (Morita et al, 2004). Other demographic details were recorded as shown in Table 5.1.2.

5.3.2.3 Measurements of effectiveness of drug treatment with anticholinergic agents

The only randomised controlled trial was placebo controlled and used a subjective rating scale of 1 to 5 as a measure of 'severity' of death rattle (Likar et al, 2002). Trained observers were reported to have rated the level of death rattle as 1= noisy

breathing, 2= slight rattle, 3 = mild rattle, 4 =strong rattle and 5 = very strong rattle together with a score of 1 to 3 as a subjective measure of observed pain and agitation. Two of the retrospective studies sought to quantify the use of anticholinergic drugs (Power and Kearney, 1992; Bennett, 1996). Two studies also sought to determine effectiveness of anticholinergic agents. Wildiers and Menten (2002) stated that the 'treatment was effective' in some patients but did not define this. Kass and Ellershaw (2003) obtained data collected from a database containing information of patients managed using the Liverpool Integrated Care Pathway for the Dying (LCP) (Ellershaw et al, 2001). The database allowed access to data collected at the time of treatment on '*response times*' which were calculated and defined as time to '*first response*' and time to '*permanent response*'. The response time for a 'permanent response' was defined as '*time from first respiratory tract symptoms until symptoms permanently absent until death.*'

5.3.2.4 Results of prospective and retrospective studies

5.3.2.4.1 Incidence of death rattle

5.3.2.4.1.1 Prospective study findings

A summary of the results of the studies appraised are shown in table 5.1.2 however some of the results are worthy of highlighting since they add significantly to the knowledge base of incidence, and aetiology of death rattle. The incidence of death rattle can be shown to vary greatly. Lichter and Hunt (1990) in a large sample of hospice patients noted a 56% incidence of death rattle, only 25% of patients required drug treatment, a further 31% requiring change of positioning, occasional suctioning, change of position and reassurance. In the same study 91.5% patients were reported to have died peacefully implying that death rattle itself did not result in a non-peaceful death. Ellershaw and co-workers (1995) did not find the association of hydration with respiratory secretions to be clinically significant but found an overall incidence of death rattle, defined as 'respiratory tract sounds' to be 92% (n=82). Back and Jenkins (1997) reported an incidence of death rattle of 43%. Hughes and co-workers (2000) noted an incidence of 'retained secretions' or 'death rattle' as reported by the number of patients receiving anticholinergic

treatment of 44%, 31% and 50% in three different groups of patients respectively each receiving a different anticholinergic (n=37 in each group). Morita and co-workers (2000) found an incidence of 44% of death rattle (n=107). Back and co-workers (2001) found an incidence of respiratory tract secretions of 44% (n=294) and 36% (n=210) in two phases of a study comparing hyoscine hydrobromide treatment with glycopyrronium treatment for death rattle. Morita and co-workers (2004) reported an incidence of bronchial secretions in 41% patients in the last 3 weeks of life. Taking the mean of these results gives an incidence of death rattle of 48%, or 44% if using the median value.

5.3.2.4.1.2 Retrospective study findings

Power and Kearney (1992) indicated that 44% (n=100) of patients were noted to have respiratory secretions (although this was not defined and must have been interpreted) but 77% were documented as having received anticholinergics, questioning whether the true incidence of death rattle was actually higher than 44%. Bennett (1996) stated that 50% of patients (n=94) received hyoscine hydrobromide in the last 48 hours of life, with 45% of patients receiving hyoscine hydrobromide within the last 6 hours (both infusion and injection were reported but not dose administered). Wildiers and Menten (2002) observed an incidence of death rattle of 23% (n=107) based on patient records of hyoscine hydrobromide administration (20 of 25 patients received hyoscine hydrobromide 0.25mg subcutaneously and 5 received intravenous infusion of 1 to 2.5mg over 24 hours). Kass and Ellershaw (2003) using retrospective data from the Liverpool Integrated Care Pathway for the Dying database found an incidence of 49% (n=202) of presence of respiratory secretions. A mean incidence of death rattle of 42% may be calculated from these retrospective studies.

5.3.2.4.2 Effectiveness of anticholinergic drugs

5.3.2.4.2.1 Prospective study findings

Hyoscine hydrobromide was noted to have an 'immediate effect' (not defined) in 94% patients treated (Lichter and Hunt, 1990). Ellershaw and co-workers (1995)

found 70% of patient's respiratory tract secretions could be controlled with hyoscine hydrobromide (route and dose not defined), 22% of patients having persistent symptoms. Hyoscine hydrobromide was noted to improve noise score from first report until death in 52% of patients and 58% of patients were noted to have an improved noise score 30 minutes after the first dose of hyoscine hydrobromide, however no doses were recorded (Back and Jenkins,1997). Hughes and co-workers (2000) monitored the effect of a standard treatment protocol using three different anticholinergics: hyoscine hydrobromide, hyoscine butylbromide and glycopyrronium. They found that 35% (n=37) of patients responded to the first hyoscine hydrobromide (0.4mg) injection, 54% (n=37) to the first hyoscine butylbromide injection (20mg) and 46% (n=37) to the first glycopyrronium injection (0.2mg). Overall hyoscine hydrobromide was judged to be less effective than hyoscine butylbromide and glycopyrronium in this study.

Likar and co-workers (2002) found that unconscious patients with death rattle, treated with hyoscine hydrobromide 0.5mg administered intravenously or subcutaneously, every 4 hours, had a tendency to less death rattle at 6 and 8 hours. This was a difference in mean rattle score of 0.8 and 0.7 which was not statistically significant when compared to those receiving placebo, but patients were reported to have a greater tendency towards agitation and pain. Back and co-workers (2001) measured noise scores 30 minutes after each injection, 1 hour post injection, intermittently 4-hourly up until death (administering doses of 0.4mg hyoscine hydrobromide or 0.2mg glycopyrronium). They concluded that fewer patients had reduced noise scores 30 minutes after an injection of glycopyrronium compared to hyoscine hydrobromide. Noise scores at 1 hour were found to be similar for each group.

5.3.2.4.2.2 Retrospective study findings

Kass and Ellershaw (2003) noted that of 99 patients noted to have respiratory tract sounds on the Liverpool Care Pathway for the Dying (n=202), 59 were treated with hyoscine hydrobromide for more than 4 hours and 38 (64.4%) of these patients were reported to have responded and to have died symptom free. Eighteen patients responded in less than four hours and were symptom free until death and twenty

patients died symptom free but had a response time of more than four hours. Twenty one patients (35.5%) died with respiratory tract sounds, ten patients (16.9%) were described as resistant to treatment.

5.3.2.4.3 Treatment of death rattle without drugs

5.3.2.4.3.1 Prospective study findings

Few details of non-drug treatment of death rattle were included in the studies reviewed. Lichter and Hunt (1990) commented that of the 56% of patients noted to have moist and noisy breathing, 31% required only nursing intervention rather than drug treatment. Ellershaw and co-workers (1995) reported that 3 patients out of 18 who had not responded to hyoscine hydrobromide, required suction. Morita and co-workers (2004) reported that oral suctioning was carried out in 22% of patients and bronchial suctioning in 10% of patients, three or more times a day. The suctioning procedure was noted to cause patient distress in 9% of cases, causing the authors to question the role of suctioning in the management of persistent secretions.

5.3.2.4.3.2 Retrospective study findings

No details of non-drug treatment of death rattle were reported in retrospective studies.

5.3.2.4.4 Other factors associated with the development of death rattle.

5.3.2.4.4.1 Prospective study findings

Morita and co-workers (2000) concluded that patients with brain, lung and bone malignancies were more likely to develop death rattle (n=294) and that there was no association with length of stay, age or sex. They also concluded that persistent rattle seemed to be associated with a diagnosis of lung cancer, the presence of pulmonary infection or oedema and unconsciousness. Suction was carried out in

12% patients in that series. In their later paper (Morita et al, 2004) pneumonia was diagnosed in 22% (n=69) of patients recruited into the study (n=310) and an association was made between the development of respiratory tract secretions and a diagnosis of lung cancer, or co-morbidities of pneumonia and dysphagia. There was no association found between respiratory tract secretions and co-existent oedema or pulmonary effusion.

5.3.2.4.4.2 Retrospective study findings

Bennett (1996) noted that administration of hyoscine hydrobromide was positively associated with longer duration of stay, cerebral malignancy and that patients receiving infusions were just as likely to have additional injections within the last 6 hours of life. Male gender, a diagnosis of lung cancer and a prolonged dying phase were identified as risk factors for developing 'respiratory tract sounds' (Kass and Ellershaw, 2003).

5.4 Discussion of systematic literature review

5.4.1 Overview of the systematic review process

A systematic literature review is defined as a summary of the medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine these valid studies (Bandolier, 2005a).

Of the thirteen studies retrieved using the selected search terms, only one described a randomised controlled study recruiting 31 patients.

In general the studies retrieved did not conform to the definition of cohort studies (Bandolier, 2005b) as generally no control group was used. They could be considered as case series. Because of the variability in the way in which retrieved studies were conducted it was not possible to combine the results in any

recognised quantitative method. Guidance was used from the Cochrane Handbook, section 6.8 (Green and Higgins, 2005) to evaluate the quality of the data presented in the studies appraised.

5.4.2 Study definitions and terminology

Although the retrieved studies were variable they show a trend in which there has gradually been an adoption of the terminology and methodology originally used by Ellershaw and co-workers (1995) including the definition of respiratory tract sounds and of the categorical rating scale (Back and Jenkins, 1997). The RTS definition gives researchers a tool with which to describe the death rattle in a uniform manner and the categorical rating scale, a subjective method of monitoring response to treatment. It is however questionable whether the RTS definition can be used to help the day to day management of this symptom in view of the possible different underlying aetiologies.

All of the retrieved studies concentrated on the use of anticholinergic agents as the accepted treatment for death rattle, and as an indication that the patient had symptoms of respiratory tract secretions. This assumption may be one source of detection bias, particularly in the retrospective studies.

5.4.3 Randomised controlled studies

Only one study matched this category in design (Likar et al, 2002) and was considered capable of measuring effectiveness of drug treatment against placebo. The German paper was translated. The results of this study showed a tendency towards a reduction in the combined mean death rattle score with hyoscine hydrobromide compared to placebo (saline) at 6 and 8 hours though this was not significant. This difference was described in their report as between the limits of 2.5 and 3.5, the difference between 'slight rattle' and 'mild rattle' (Scale: 1=noisy breathing to 5=very strong rattle). Although all observers were stated to have been

trained, the way in which the scoring was carried out is not clear. More frequent expressions of pain and agitation from the patients receiving hyoscine hydrobromide were also recorded. The reason for this was not clear and patients were stated to have received equipotent analgesia. Interpretation of the results of this study is difficult in terms of the subjective nature of the scoring. The authors concluded that the doses of hyoscine hydrobromide may not have been optimal for treatment of death rattle (although the bolus dose exceeds current practice in the UK). They suggested further studies using higher doses of hyoscine hydrobromide in addition to analgesia and sedative drugs. The number of subjects was small. The randomised controlled double blind aspect of the study design however appeared to be feasible to study death rattle, allowing that after 12 hours the study was carried out in an open fashion and drugs continued if necessary. It was not clear that consent was obtained for this study however. Drug treatment for death rattle was stopped after 24 hours if no difference was seen in response to the death rattle.

5.4.4. Retrospective case series

Although the design of the retrospective studies have been useful in estimating incidence and current practice with regard to treatment of death rattle, the quality of patient records and reporting habits of the health care professionals vary greatly depending on the centre. Bennett (1996) noted that the patient's medication chart and the recorded admission and death dates were considered more reliable sources of information than records (in the medical notes) of concomitant disease and metastatic disease.

With regard to selection bias, as long as the demographics of the population have been described, the palliative care populations may be compared and assessed. Consecutive death recording differs from admissions data, however where the outcome being studied is death and dying symptoms, this difference is probably not significant.

Detection bias however may be an issue with regard to how much interpretation was made of the raw data, the quality of recording and completeness within the

data. The retrospective method used by Kass and Ellershaw (2003) requires further discussion. Although the data was reviewed retrospectively, the method of data collection was prospective, standardised and specific to the use of the Liverpool Integrated Care Pathway for the Dying, the treatment protocols used within that pathway of care and the maintenance of the database. Where this pathway is used, nursing staff are trained to use the pathway to record all care during the dying phase. The possibility of performance bias arising from this method results from the fact that patients will often 'automatically' be prescribed an anticholinergic agent in anticipation of development of respiratory tract sounds. This in turn may lead to an increase in the proportion of patients who would receive anticholinergics.

5.4.5 Prospective case series

The selection of patients included in the prospective studies was a possible source of selection bias as usually this was not randomised. This may be minimised by careful description of population demographics. The only exception to this was the study by Lucas and co-workers (1994) which was a preliminary study with only 11 patients, a sample size from which was too small to draw conclusions. The estimated incidence of death rattle found in all of the retrieved prospective studies was similar in most cases to those with a retrospective design, being between 40 and 50% of patients, with only one estimate of 92% falling outside this range (Ellershaw et al, 1995). The design of this study (Ellershaw et al, 1995) focussed on assessment of the level of hydration of the patient with respect to respiratory secretions. There was the possibility for selection bias in the study admission criteria. Patients were admitted to the study after daily review and admission criteria included patients who were unable to take oral medication or were only able to take sips of fluid. This would not seem to be an unreasonable criteria for study inclusion and should mirror normal practice of prescribing review for these patients. It may however have had the effect of increasing the proportion of patients prescribed anticholinergics for secretions over 'usual' practice. There is also a possibility that the fact that the study was in process, may also have been a cause of increased reporting of respiratory tract secretions leading to performance bias. An audit of anticholinergic treatment (Hughes et al, 2000) included only 37 patients per

treatment group, however this was designed as an audit and as such is valid. Numbers may be too small however to draw significant conclusions about treatment effect. Possible confounding factors (such as infection, pulmonary oedema, refluxed gastric contents) were however recognised and their input was acknowledged.

The study by Morita and co-workers (2000) could have been affected by performance bias as no strict treatment protocol of death rattle could be adopted owing to ethical considerations. In interpreting treatment effects in studies of palliative care, the differences in cultural treatment practices should be born in mind and accounted for, particularly when comparing studies in different countries. Differences may be in terms of accepted cultural practice such as route of drug administration, use of suction, or routine availability of medication. Morita and co-workers (2004) excluded a large number of categories of patients including those with renal failure (not defined), hypercalcaemia, endocrine disorders, recent tumour treatment, and communication difficulties such as aphasia or aphonia. This makes the generalisability of these results to a normal palliative care population more difficult and the authors conclusion that that bronchial secretions develop in 40% of *all* dying patients must be interpreted with caution. However, the use of a similar approach in terms of definition and monitoring in the study (Morita et al, 2004) provides more comparable data.

Outcome data from the prospective studies regarding the efficacy of anticholinergic treatments was conflicting. Hughes and co-workers (2000) concluded that hyoscine butylbromide and glycopyrronium were more effective than hyoscine hydrobromide. Hyoscine hydrobromide was however the gold standard used by Back and co-workers (2001) to compare against glycopyrronium, where both agents were found equally effective at one hour. The authors however noted the reduced number of patients recruited in phase two of their study in which the glycopyrronium injection was the drug studied compared with phase one, where hyoscine hydrobromide was assessed. The authors considered the cause to be 'research fatigue' which could result in selection bias. Indeed a response by Murtagh and co-workers (2002) to this study commented on this aspect of the study together with the possibility that the increased use of other drugs including midazolam could be accounted for by the fact that patients recruited into the second phase of the study were more ill,

rendering the glycopyrronium apparently less effective. This also questions the comparative dosing regimen of hyoscine hydrobromide and glycopyrronium chosen.

Throughout the studies there was a notable lack of recording of any possible side effects attributable to the anticholinergic agents. It must be appreciated that palliative care patients may be on a number of drugs making it difficult to attribute side effects to any one, or indeed distinguish them from the disease process. Power and Kearney (1992) noted agitation in patients receiving hyoscine hydrobromide, which may have had other underlying causes. Likar and co-workers (2002) also noted increased restlessness and more pain in the group receiving hyoscine hydrobromide. In many of the studies it is not clear whether no adverse effects occurred during anticholinergic treatment or whether any adverse effects were not noted or recorded.

5.4.6 Summary. Evidence from the literature for the benefits of anticholinergic treatment of death rattle in palliative care.

The studies retrieved and appraised represented the current literature and state of knowledge of the incidence and drug treatments administered for death rattle. The standard treatments used are anticholinergic drugs. The incidence of death rattle appears to be between 42% and 48% in patients dying in palliative care units. Patients with a primary diagnosis of lung cancer, underlying pneumonia and dysphagia and patients with a prolonged dying phase may have a higher incidence of developing death rattle. The efficacy of anticholinergic drug treatment in the treatment of death rattle is difficult to assess from these studies due to the variability of outcome measures and differences in study design. Adverse effects which may be attributable to anticholinergic therapy have been described, but many studies did not record adverse effects.

The literature demonstrates many of the problems with assessing symptomatic treatment in palliative care and the resulting poor levels of evidence to support effective treatment of death rattle. Many of the underlying problems are ethical in

origin and will be discussed later in Section 10.2, others are of a more cultural nature and demonstrate the complexity of treatment interventions in palliative care. These problems will be discussed in more depth in the general discussion (Chapter 10).

6 Results from ethical consultations with nursing and medical staff

6.1 Introduction to ethical consultations

During the methodology development stage of the present study, focus groups were held to determine underlying feelings of the nursing and medical staff who would be involved with consenting and monitoring patients during the study. As the focus groups were part of the developmental stage of the project, instigated in order to collect information regarding methods of data collection rather than requiring complete analysis, field notes were taken to record the major issues arising from the interactions. The overall aim of this part of the study was to investigate underlying opinions and gain feedback on the intended methodology in the palliative care in-patient setting.

Each focus group began with a standard presentation of the proposed study methodology (by CH) followed by group discussion. The aims and objectives of the study were presented to the group (Chapter 3). The procedure for consent was then introduced for discussion, followed by an introduction of the proposed monitoring forms and the procedure for monitoring. The procedure for conducting the face to face interview with patient's relatives whilst the patient was being treated for death rattle was discussed together with a draft of the proposed questions. The patient information leaflet and consent forms were circulated for comment. At this point the Ethics committee (MREC) had not returned any decision regarding the method of objective 'recording' of the death rattle noise, therefore both noise meter and sound recording were discussed as possible monitoring tools. Field notes were recorded during and after the meeting to record the significant issues.

6.2 Results from the ethics consultation focus groups

Five focus groups took place over two different Hospice sites, Hospice 1 and Hospice 2:

Group 1 consisted of 20 hospice staff including medical staff, home care nursing team members and in-patient nursing staff. (Hospice 2)

Group 2 included five evening nursing staff (Hospice 2) Group 3 and Group 4 and Group 5 involved groups of 5 to 6 day nursing staff including auxiliaries in Hospice 1.

Comments from the meeting with the research committee of Hospice 2 are also included. The resulting comments from these groups were used to mould and underpin the methodology of the present study and are represented below.

6.2.1 Palliative care team overview

Although all staff appeared generally supportive towards the study and expressed a willingness to take part, there were also some anxieties expressed about how this might affect their role of caring for the patient and their family.

This was expressed as:

“worry about impinging on the patient or relative relationship at this difficult time”

and

“intrusion in the caring continuum”

in discussion relating to conducting the consent process and during the act of collecting outcome measurements and carer interviews.

These views were acknowledged as a potential problem, but staff were reassured that for potential patient and relative groups where it was considered that the anxiety caused by any consent or monitoring procedure would be unacceptable, that these patients or families would not be approached to be included in the study. Staff required reassurance that if circumstances during monitoring became such that continued monitoring, after a patient had been consented and entered into the study, was inappropriate because of family anxiety, that the monitoring procedure could be modified to become subjective only.

The groups felt that the present study might focus relative's attention on death rattle resulting in problems in bereavement. It was agreed that this issue would be

followed up with the bereavement workers so that support could be offered if required.

6.2.2 Views about the patient carer questionnaire for face to face interview

Some of the original wording of the draft questions to guide the face to face interviews was described by one group member to be '*pious*' and '*patronising*'. The wording was therefore altered to accommodate the feedback.

Initially there was discussion about whether the nursing would be able to carry out the face to face interviews with the carers, whilst the patient was being treated for death rattle. However the nursing staff in all groups expressed concern that the present study might be "*opening a can of worms*" in this respect. It was felt that the interview might take an excessively long time if carried out by nursing staff and could result in continued focus of relatives on the death rattle if the nurse was continually caring for the patient. It was decided therefore that face to face interviews with relatives would not be carried out by nursing staff involved in the daily care of the patient but would be carried out by CH or the medical staff.

6.2.3 Acceptability of sound recording or noise meter monitoring of death rattle to ward staff

There was almost overwhelming opposition from the nursing staff to the suggestion of making a sound recording of death rattle.

Comments made included:

"nurses would like a get-out clause so that they did not have to approach relatives who were too distressed" with regard to measuring or monitoring noisy breathing levels"

and

"what if we record their last breaths?"

There was concern that relatives at the bedside would feel inhibited

“will relatives feel they can’t talk?”

Although the last two comments were clearly directed against the suggestion of recording sound using a minidisc recorder, the first comment regarding distressed relatives and monitoring in general could also have applied to the use of the noise meter.

It was explained that the noise meter would not record sound and that this would be explained to the patient. Nursing staff required further reassurance that objective noise level monitoring could be suspended if the family became too distressed and wished monitoring to be discontinued.

6.2.4 Positive comments and suggestions in support of the study

Overall there was support for the study and the following comments balance the negative, in looking for solutions to some of the objections detailed above:

“Start from day one [taking consent] then it would not be an issue to introduce at the end.”

Early consent of patient’s to take part in the present study was considered to be a good idea by both nursing and medical staff and there was agreement that this should be done early on in the admission. It was commented however that consent on admission might infer that the patient would not leave the hospice, which might create anxiety for the patient and relatives or carers. A proposal to consent only those patients admitted for terminal care or ‘continuing care’ was suggested.

The nursing staff were reluctant to be involved in the consent process. Reasons given for this included that nurse consenting could introduce bias into the study. It was discussed that nurses could be trained to consent the patients, however they felt uncomfortable at the suggestion of consenting the patients. Some nursing

staff did however volunteer that they might be able to consent relatives for the face to face interview, with the appropriate training.

There was a suggestion that posters could be put up around the ward environment informing patients that research was taking place and that they may be approached for consent into the study at admission. This suggestion was utilised, in that posters outlining the study procedure were placed in clinical areas for the purpose of reminding medical and nursing staff. It was considered that a more public display of information in poster form in areas of public access within the hospice, for this particular study on death rattle, could cause anxiety in some patients and visitors without the accompanying explanation and information leaflet.

A nurse who had returned to hospice nursing after a period away expressed that:

"coming back to hospice nursing, I have a different and perhaps less protective outlook to this type of research"

6.2.5 Summary of the pre-study findings from focus group work on ethical issues surrounding the study methodology.

Overall the opinions voiced within all the groups conducted supported the present study and the methodology as long as the reservations voiced were acknowledged. It was concluded that consent would be taken, where possible, by medical staff whilst admitting patients to the hospice for terminal care. Nursing staff generally expressed an unwillingness to be involved in the consent procedure.

With regard to monitoring, a compromise was made to utilise the noise meter as an objective measure of sound level as the sound recording using the minidisk recorder was felt to be too intrusive. It was agreed that objective measurements could be suspended if the family expressed that this caused them anxiety. It was agreed that the carer interview would be performed by CH or medical staff.

The views expressed by the Ethics committees and the nursing staff did not always agree on what was best for the patient and their family. There will be further discussion following the results of the present study on ethical issues brought together in the general discussion (Chapter 10).

7 Results of noise monitoring of death rattle (Hospice 1 and Hospice 2)

Part A. Results from the validation of the noise meter.

7.1 Introduction

In order to introduce an objective system for measuring changes in the level of death rattle noise in response to administration of anticholinergic drug treatment, a noise meter, measuring loudness of sound in decibels (dB) was chosen. Although an alternative method of monitoring sound by recording death rattle sounds onto a minidisc had been considered, the results of focus group discussion during the developmental stages of the present study together with responses from the Ethics Committee (MREC) supported only the use of the noise meter.

Before proceeding to use the noise meter as a monitoring tool, a validation exercise was carried out to ensure that the meter could be used easily by the nursing staff to measure the death rattle sound under investigation and that the noise meter was capable of detecting the sound of death rattle and provide readings which would be reliable within the study environment. It was also necessary to demonstrate that the meter would provide readings which would differentiate over the range of breath sounds from quiet breathing sounds to death rattle sounds. The readings would be in addition to the subjective noise scoring of 1 to 3 on the data collection form (Appendix C). In order to validate the noise meter, a sound recording of a death rattle noise was made and multiple readings taken at specified distances from the noise source under controlled conditions as explained in Section 4.6.4.

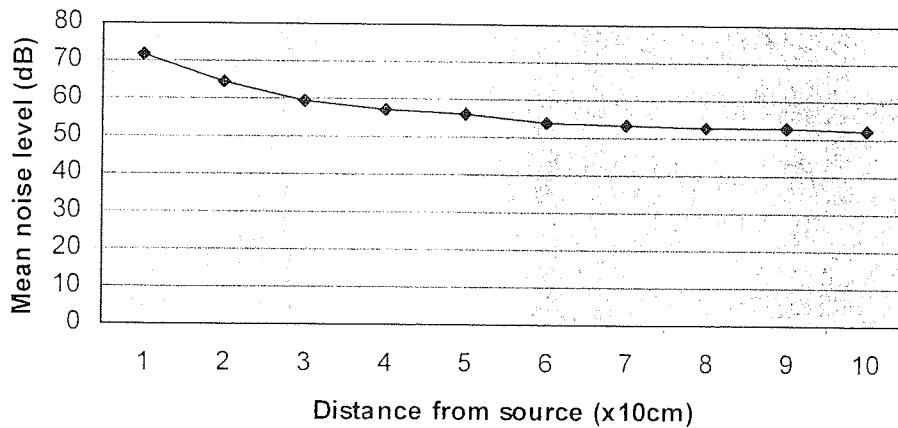
7.2 Results from noise meter recording of simulated death rattle noise and breath sounds at increasing distances from the noise source.

Data was collected at increasing distances of 10cm from the noise source of mimicked death rattle, from 10 to 100cm, along the axes as described in methods figure 4.6.4.1. The mean of the noise level readings (dB), with increasing distance from the noise source along axis 4 (Table 4.6.4.1) are shown in Table 7.2.1 and Figure 7.2.1 as examples. Results for noise levels recorded along all axes 1 to 7 are shown in Appendix G.

Table 7.2.1 Mean noise level in decibels (dB) with increasing distance from the recorded death rattle sound (Axis 4)

Distance from source	Noise meter readings in decibels (dB)					Mean noise level
	Reading 1	Reading 2	Reading 3	Reading 4	Reading 5	
10cm	74.8	71.3	71.2	71.1	71.2	71.92
20cm	64.6	63.3	62.9	64.4	65.8	64.2
30cm	60.4	60.1	58.7	58.4	59.1	59.34
40cm	59.3	56.3	57.6	56.9	57	57.42
50cm	56.3	55.8	56.2	56.7	56.8	56.36
60cm	55.6	54.1	53.8	53.2	53.4	54.02
70cm	55.6	53	52	52.5	53	53.22
80cm	53.8	52.4	52.4	52.6	52.2	52.68
90cm	52.9	51.9	52	52.8	53	52.52
100cm	52.1	52.4	52.9	52.1	51.4	52.18

Figure 7.2.1 Mean noise level reading in decibels (dB) with increasing distance from the recorded death rattle sound (Axis 4)

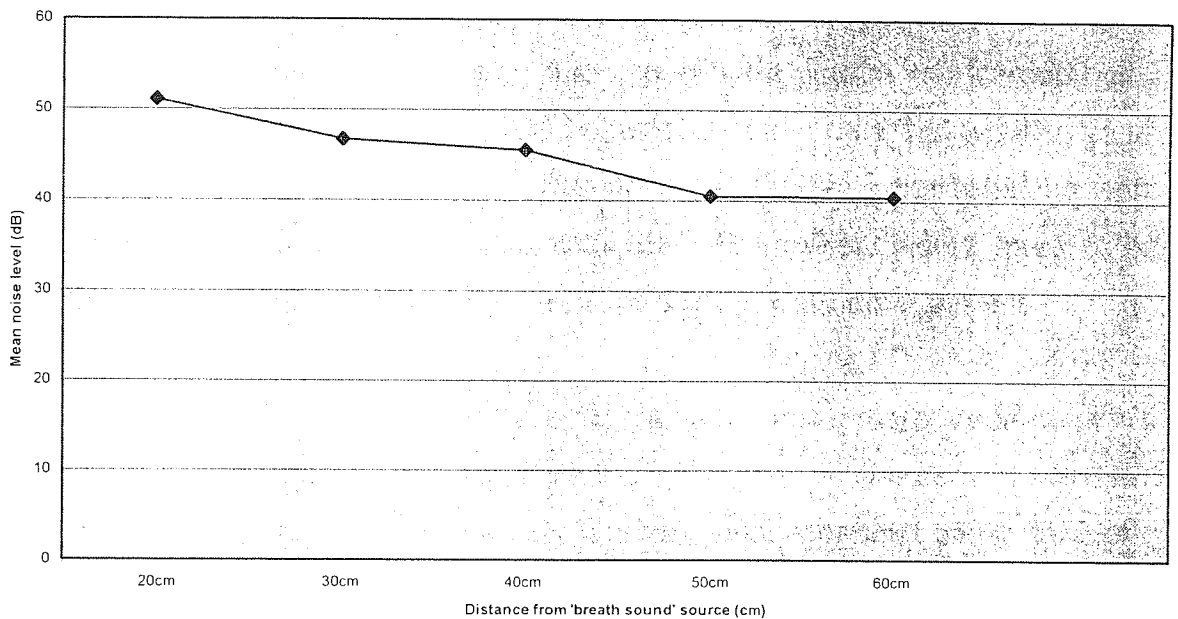


Noise levels were also measured for a 'breath sound' noise source. This was not repeated along all axes. Results for this are shown in Table 7.2.2 and Figure 7.2.2.

Table 7.2.2 Mean noise meter readings (dB) at the specified distances from the recorded 'breath sound'

Distance from recorded breath sound (cm)	Mean noise reading (dB)
20	51.14
30	46.73
40	45.6
50	40.5
60	40.4
70	Lo
80	Lo

Figure 7.2.2 Mean noise level reading in decibels (dB) with increasing distance from the recorded breath sound (Axis 4)



The noise level readings (in decibels) of the death rattle sound and the breath sound declined in a linear fashion with increasing distance from the noise source. This was true for the death rattle sound along any of the axes 1 to 7.

Figure 7.2.2 and the data in Table 7.2.2 shows the decline in noise meter readings in decibels with increasing distance from the 'breath sound' noise source. At a distance of 70cm however, the noise reading for breath sound was below the range of the noise meter (40-130dB). At a distance of 40cm from the recorded noise source the maximum noise level reading was 48dB.

7.3 Discussion of the noise meter readings at increasing distances from the simulated death rattle noise and breath sounds.

The validation of the noise meter using a recorded noise source was carried out in order to show that the noise meter could be used to obtain data that would give an objective measure of the noise level of death rattle. Further considerations were that method of measuring noise level with the noise meter, would have to be acceptable to the nursing staff and be easily used in the ward environment.

As expected, the noise level recorded in decibels by the noise meter decreased in a linear fashion with increasing distance from the noise source. The decibel scale is a logarithmic scale, named after Alexander Graham Bell, a decibel being 1/10 of a bel.

Our perception of sound is governed by the amplitude or intensity of the sound wave. The Bel represents a tenfold increase in sound, the human hearing able to hear over a range of 12 Bels. An increase of 6dB (decibels) represents a doubling in perceived loudness. Most people are able to just perceive a change of 3 dB. Examples of approximate levels of sound in decibels would be represented by 10dB for the rustling of leaves, 20dB for a whisper, 40 dB for the average noise level at home and 50dB for a normal conversation. A busy shop would be expected to have a sound level of approximately 60dB and a jet aircraft taking off 120dB.

To allow noise level measurements to be taken quickly and reproducibly, and for this method to be acceptable to the nursing staff for continual recording of noise data, the distance from the noise source (the patients mouth) needed to be the maximum distance from the mouth which would give reliable readings, so as not be intrusive to the patient and relatives and be easily measured.

At 40cm the combined mean noise meter reading over all seven axes for the death rattle noise source was 58.3 dB (Maximum 62.7dB) and for the breath sound a mean of 45.6 dB and maximum of 48dB. This represents a difference of over 12

decibels between breath sound and rattle noise, thus providing a measure which corresponds to a difference which could be perceived by the human ear and should provide an objective measure for reduction in rattle noise.

It was therefore decided that the nursing staff should take noise meter readings 40cm away from the noise source. The noise level measurement to be taken as the highest noise meter reading over three breaths.

Although still a linear decline in mean noise level, occasional readings taken at less than 40cm from the recorded noise source seemed unusually high. This may have been due to the sampling frequency of the noise meter and the inconsistent nature of the death rattle noise, causing the meter to register large changes in amplitude at distances less than 40cm from the noise source.

7.4 Conclusion

The results demonstrated that the noise meter could be used to differentiate between breath sounds and the level of noise from a simulated recorded death rattle sound and provide an additional objective outcome measure for treatment interventions. Taking noise level measurements at a distance of 40cm from the patient as described in the protocol (Appendix D) should provide an acceptable measurement distance from the patient in terms of not being too obtrusive for the patient, and should provide acceptable objective noise level results.

7 Part B: Results of individual patient case noise monitoring of death rattle (Hospice 1 and Hospice 2)

7.5 Comparison of environment at each hospice

The initial aim of the present study was to recruit patients from more than three hospices in the West Midlands. However owing to the time taken to obtain ethical approval combined with the logistics of maintaining recruitment and monitoring, data was collected at two hospices only. The reasons for this and the implications for this study will be explored more fully in the discussion.

Noise monitoring data was collected from patients recruited to this study at two hospices in the West Midlands. Hospice 1 was a 22-bedded voluntary funded, inpatient unit. Medical services, at the time of the study, were provided by two full-time Consultants in Palliative Medicine, (one of whom was the Medical Director of the hospice), together with an associate specialist, a specialist palliative care registrar (on rotation), and a senior house officer (on rotation for six month periods). All hospice in-patients were reviewed on ward rounds which were carried out on three days of each week. Specialist palliative medicine doctors were available on the hospice premises during working hours and available on-call at night. Hospice 1 also housed a day-care unit and a Home Care Team of clinical nurse specialists who provided support for patients known to the hospice service in the community and support for community health care professionals. Hospice 1 was situated in the suburbs of a large West Midlands City but served a population living over a wide geographical area ranging from inner-city to more rural settings.

Hospice 2 was a 27-bedded voluntary funded inpatient unit. Although Hospice 2 did not have a palliative care consultant in post at the time of this study, medical services were provided by two staff grade doctors with specialist knowledge and experience in palliative medicine together with part-time medical cover from General Practitioners and Senior House Officer Grades with an interest in palliative care. Hospice 2 had access to advice from a Consultant in Palliative Medicine. All

hospice in-patients were reviewed twice weekly at ward rounds, one of which was multidisciplinary. The specialist palliative medical staff attached to the hospice were available on the hospice site during the day and on-call out of hours. Hospice 2 also housed a day-care unit and a Home Care Team of clinical nurse specialists. The hospice was situated in a major city in the West Midlands taking patients mainly from urban areas.

Neither hospice had a written protocol for treating death rattle at the time of this study, therefore the study data observed and recorded was based on 'current normal practice' in the treatment of death rattle at each hospice.

At Hospice 1, patient recruitment took place from March 2002 to December 2003 (21 months) at Hospice 2 recruitment took place from November 2002 to December 2003 (13 months). Patient recruitment was initiated at Hospice 1 being the base hospice of CH. The delay in starting the study at Hospice 2 was related to staffing issues.

7.6 Comparison of hospice demographic data

The comparative data from each hospice for inpatient admission, deaths and average duration of stay are shown in Table 7.6.1. Data was obtained from each hospice's database via their respective information departments. The study recruitment and data collection periods were not equal in terms of time. Recruitment began in each hospice after ethical approval and appropriate training had been given to staff; this was achieved earlier in Hospice 1.

Table 7.6.1 Comparison of patient admissions, deaths and average duration of hospice stay for the two hospices

Hospice	Hospice 1	Hospice 2
Data collection period	March 2002 to December 2003 (21 months)	November 2002 to December 2003 (13 months)
Number of inpatient admissions	458 (214M:244F)	468 (248M:220F)
Number of inpatient deaths	330	241
Mean duration of stay	21 days	14 days

The total number of in-patient admissions to each hospice during the respective study periods were 458 for Hospice 1 and 468 for Hospice 2, although the duration of the study periods were different. From these figures, Hospice 1 admitted a mean of 22 patients per month and Hospice 2 a mean of 36 patients per month. The number of inpatient deaths recorded was a similar proportion of the admissions for Hospice 1 (16 per month) and Hospice 2 (18 per month). The ratio of male to female admissions varied between the hospices, being 1:1.4 (M:F) in Hospice 1 and 1: 0.88 (M:F) in Hospice 2 during the study period. The recorded average length of stay, obtained from hospice data, during the time period of this study was of shorter duration for Hospice 2 than Hospice 1.

Table 7.6.2 Comparative data by ages of admission and diagnosis of primary cancer sites for the two hospices.

Background Data for hospice inpatient admissions	Number of inpatient admissions to Hospice 1 (N=458)		Number of inpatient admissions to Hospice 2 (N = 468)	
	Male	Female	Male	Female
Patient Ages				
<15 years	0	0	0	0
15-24 years	4	0	3	0
25-64 years	77	110	92	75
65-74 years	59	50	68	55
75-84 years	54	67	47	53
>85 years	20	17	21	21
Not known			17	16
Total	214	244	248	220
Primary diagnostic cancer site				
Breast, bone, connective tissue, skin	9	53	10	43
Buccal cavity, pharynx	4	2	31	15
Digestive, perineum	63	63	52	62
Genito-urinary	56	34	51	25
Lymphatic & haemopoetic tissue	5	4	15	11
Respiratory	40	39	45	37
Secondary	6	2	0	0
Not known (recorded)	5	9	9	10
Other sites	19	32	15	6
Death Non cancer	7	6	20	11
Total	214	244	248	220

The proportion of admissions in each age group were similar between each hospice although more females were admitted in the 25-64 and 75-84 year-old age group in Hospice 1. More males were admitted in the 25-64 and 65-74 year old age group in Hospice 2 during the study period. The age data for Hospice 2 contains unrecorded ages as some of the admissions were re-admissions and were not counted twice on the hospice information system. In Hospice 2 there

was a higher proportion of admissions with primary oropharyngeal and haematological malignancies.

7.7 Number of patients consented for entry into the present study

Some small adjustments were required to the established methodology as this study commenced. Although it was intended that all patients who were considered to be potentially eligible for recruitment into the present study would be consented on admission to the hospice, in practice this proved difficult for reasons that will be discussed later. In both hospices therefore, potential patient recruits were identified for consent at multidisciplinary ward rounds which took place once or twice weekly in both hospices.

It also became apparent within the first few weeks of the patient recruitment for the present study at Hospice 1, that some patients who may have been potential candidates for the study were not being consented, but did receive treatment for death rattle and were therefore unintentionally excluded from the study. It was important to determine firstly why this had happened and to encourage consenting of patients and secondly to establish the number of patients who were treated with anticholinergics for death rattle but not entered into this study.

At both hospices patient's medical records were examined retrospectively, firstly to make sure that all of those patients consented for the study had been identified, and secondly to attempt to determine the number of patients who had received anticholinergics but who had not been consented into the study. At Hospice 1 this was achieved by retrospective checking of all patient case notes and drug administration records of those with a date of death recorded in the admissions diary during the study period. At Hospice 2, the patients medical records and drug administration charts of all patients admitted during the study period (recorded by CH) at regular ward round attendance, were reviewed retrospectively. Anonymous data was collected of the number of patients who had received anticholinergic drugs, reportedly for death rattle.

Table 7.7.1 Overview of patients consenting to the study in each hospice and the extent of monitoring and administration of anticholinergic medication for death rattle.

Hospice	Hospice 1	Hospice 2
Number of admissions during study period	458	468
Number of deaths during study period	330	241
Number of patients consented	35	41
Number of patients consented, anticholinergics administered and some data recorded. (Group 1)	14 (40% of those consented)	21 51 % of those consented)
Number where noise meter used	7	9
Number of patients with a relative interview	4	4
Number of patients consented, where anticholinergics administered but no monitoring performed. (Group 3)	4	9
Number of patients consented but did not need anticholinergics. (Group 2)	16	11
Number of patients consented and lost to follow-up.	1	0
Number of patients not consented but to whom anticholinergics were administered for death rattle. (Group 4)	98	78

The number of patients consented in each hospice was very small considering that the aim was to consent on admission. Only 7.6% of all admissions were consented for the study in Hospice 1, representing 10.6% of subsequent deaths and 8.5% admissions were consented in Hospice 2, representing 8.7% of subsequent deaths.

It was only possible to monitor (to a greater or lesser extent) the outcome of anticholinergic treatment in 40% and 51% of those patients consented at Hospice 1 and 2 respectively. Only four patient's relative or carer interviews were carried out in each hospice.

The quality of data recording varied considerably between the two centres and between patients. At the outset of the present study it was hoped that all patients would have subjective noise and objective noise monitoring performed before and during anticholinergic treatment, however the data in Table 7.7.1 and Figure 7.7.1 and 7.7.2 show that this was not the case in either hospice. The reasons for this and the effect on the study will be considered in the discussion Section 7.14.3.

From this data it appears that 35% of dying patients received anticholinergics in Hospice 1 and 39% received anticholinergics during the study period in Hospice 2.

Figure 7.7.1 Patients in Hospice 1. Overview of monitoring outcome for treatment of death rattle compared with inpatient deaths

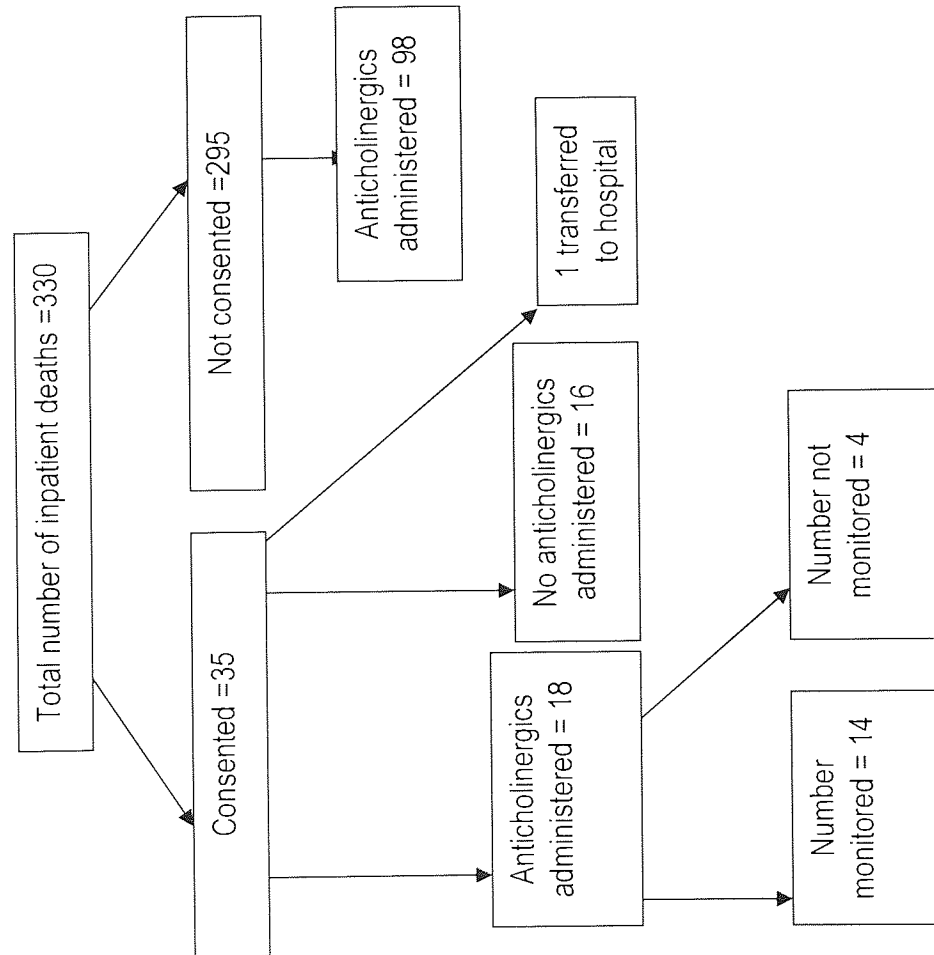
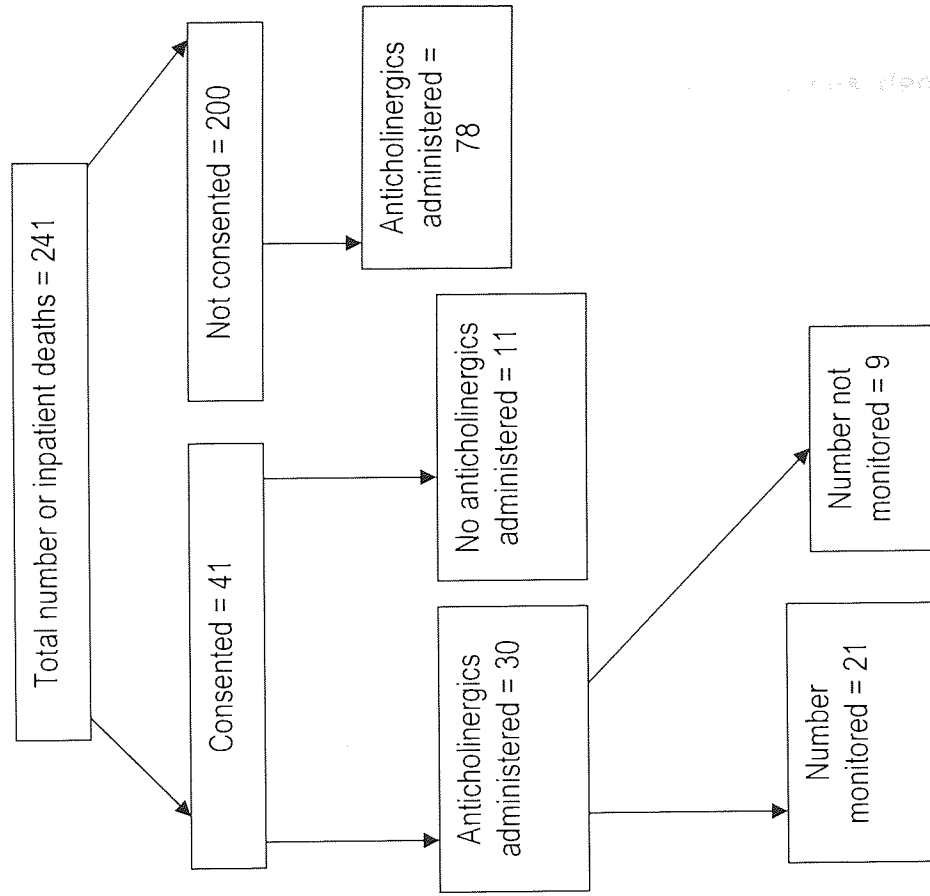


Figure 7.7.2 Patients in hospice 2. Overview of monitoring outcome for treatment of death rattle compared with inpatient deaths.



The retrospective check of patient medical records in both hospices identified 98 patients in Hospice 1 who had received anticholinergic drugs for death rattle but had not been consented and recruited into the study and 78 patients in Hospice 2. Although the retrospective check was a valid method of determining that all recruited patients had been accessed it did not achieve complete retrieval of all medication records. This method of data collection could not therefore be regarded as robust and valid for this purpose, but gives an indication of the number of patients lost to recruitment.

7.8 Characteristics of patients who were recruited into the study, received anticholinergic treatment and were monitored

The sections which follow, detail and review the characteristics and observations recorded of the sub-group of patients who were administered anticholinergics for the treatment of death rattle and were monitored to observe outcomes of treatment (14 patients in Hospice 1 and 21 patients in Hospice 2).

7.8.1 Primary diagnosis of recruited patients who received anticholinergic treatment and were monitored

The most prevalent primary cancer diagnosis in the group of patients who received anticholinergics was carcinoma of the lung (n=8), followed by tumours of the digestive tract (n=6) and buccal cavity and pharynx (n=6). This was not representative of the proportion of patients with each diagnosis admitted to the hospices (Table 7.8.1). The group of patients, treated with anticholinergics, included a greater proportion of patients with oropharyngeal and lung tumours. None of the patients in this sub-group had a primary diagnosis of non-malignant disease.

Table 7.8.1 Tumour type of those patients who received anticholinergics, with recorded treatment outcomes.

Tumour type	Hospice 1	Hospice 2
Lung	4	4
Ovary	0	2
Prostate	0	1
Brain, neurological	1	2
Digestive tract	1	5
Buccal cavity,pharynx	4	2
Skin	0	1
Breast	0	0
Other	3	2
Haemopoetic	0	1
Unkown primary	1	1
Total	14	21

7.8.2 Factors which may have influenced whether patients were administered anticholinergic agents for the treatment of death rattle.

From previous studies certain risk factors such as pulmonary infection, primary diagnosis of lung cancer (Morita et al, 2000), also a prolonged dying phase (Kass and Ellershaw, 2003) have been associated with the development of death rattle in patients dying in palliative care institutions. Some of these factors were included on the baseline data monitoring sheet to be completed on entry of the patient into this study (Appendix C). Data was also collected on whether the patient was in a single room, whether any explanation regarding death rattle had been given to relatives and the conscious state of the patient to determine whether the environment that the patient was nursed in, influenced whether anticholinergic drugs were administered for death rattle. Other underlying pathologies, have also been identified as risk factors for developing death rattle, these are reported in Section 5.3.2.4.4.

7.8.2.1 Influence of the number of patients per room on the administration of anticholinergics for death rattle.

It was postulated that the nursing environment and the proximity of other patients might affect the likelihood of a patient receiving anticholinergic drugs in an attempt to control death rattle. The nursing environment of the patients entered into this study and monitored is shown in Table 7.8.2.1

Table 7.8.2.1 Nursing environment of patients who received anticholinergics with recorded treatment outcomes

Room Size	Hospice 1 Consented patients receiving anticholinergics	Hospice 2 Consented patients receiving anticholinergics
1 bed	2	13
2 or more beds	10	8
Not recorded	2	0
Total	14	21

The data only address those patients who were recruited into the study and were given anticholinergics. It is acknowledged that some patients developing death rattle may have been moved from a multi-bedded ward into a single room to avoid disturbing others. As a result of such a move it may have been decided that drug treatment of death rattle was unnecessary. There is a possibility that patients already in single rooms, who develop death rattle may not receive anticholinergics (particularly if no relatives are present at the time) and therefore the possibility of bias in this data. Many more patients entered into this study at Hospice 2 were nursed in single rooms.

7.8.2.2 Influence of explanation of death rattle given to relatives and carers

Information was sought on whether the patient's attending relatives or carers had been given an explanation for the cause of the death rattle – this implied information given by the nurses, data which could therefore be easily captured by

the nurse recording the baseline data for entry into the study (Appendix C). The majority of responses from the data recording chart were 'yes' or 'don't know'. A response of 'no' was only given when no relatives were present. However, this process did not record the extent of any extra verbal explanation or indeed the content of such explanation.

7.8.2.3 Influence of the level of consciousness of the patient on anticholinergic treatment received

The level of consciousness of those patients entering the present study varied in both hospices. The numbers are too small to be of statistical significance but there were more patients in the unconscious and fluctuating categories, combined than in the conscious category. This is not unexpected in this group of patients.

Table 7.8.2.3 Effect of the level of consciousness of patients who received anticholinergics with recorded treatment outcomes

Conscious level	Hospice 1	Hospice 2
Conscious	4 (29%)	6 (29%)
Unconscious	5 (36%)	6 (29%)
Fluctuating	2 (14%)	9 (42%)
Not recorded	3 (21%)	0
Total	14 (100%)	21 (100%)

7.9 Anticholinergic prescribing and administration to patients consented for the study in each hospice

7.9.1 Anticholinergic drug usage differences between Hospice 1 and Hospice 2

The two hospices participating in this study have historically developed their individual common practice on the administration of anticholinergics for the treatment of death rattle. Neither of the hospices had a written policy or protocol for the treatment of death rattle. Basic differences in the therapeutic approach to drug treatment of death rattle existed between the two hospices which is characterised

by the data gathered from the treatment records of patients treated in this study and these are shown in Table 7.9.1.

Treatment was individualised for each patient in response to symptoms but the table demonstrates the trend towards use of single bolus subcutaneous injections of hyoscine hydrobromide (HHBr) at Hospice 1 in comparison to an increased use of syringe drivers to deliver subcutaneous infusions and a predominant use of hyoscine butylbromide (HBBr) at Hospice 2.

Table 7.9.1 Anticholinergics prescribed for patients consented and monitored in the study

Anticholinergic drugs administered	Hospice 1 No. patients consented and monitored given at least one dose	Hospice 2 No. patients consented and monitored given at least one dose.
Bolus HHBr 400mcg only (repeated)	10	0
HHBr Sd 1.2mg only	2	0
HHBr bolus + Sd HHBr	0	0
Bolus HHBr then Bolus GLY(200mcg)	1	0
Bolus HHBr or Sd HHBr followed by Bolus GLY	1	0
Bolus GLY 400 mcg	0	0
Bolus HBBr 20-40mg	0	6
Bolus HBBr + Sd HBBr	0	7
Sd HBBr 120mg/80mg	0	4
Bolus HBBr + sd HBBr then Bolus GLY	1	7
Bolus HBBr 20mg then Bolus GLY then sd HBBr	1	0
Bolus HBBr and Bolus GLY	0	1
Bolus HBBr followed by Bolus GLY	0	11
Sd HBBr followed by Sd GLY	0	1

Key: Anticholinergics drugs prescribed

HHBr = hyoscine hydrobromide

HBBr = hyoscine butylbromide

GLY = glycopyrronium

Bolus = bolus subcutaneous injection

Sd = syringe driver administering subcutaneous infusion over 24 hours

Hyoscine hydrobromide, administered by bolus subcutaneous (sc) injection was first line treatment for excess secretions at Hospice 1 (In 10 (71%) patients). Hyoscine hydrobromide was administered by subcutaneous infusion via a syringe driver over 24 hours to only two of the consented patients at Hospice 1. Two patients at Hospice 1 were administered hyoscine butylbromide (one by infusion and bolus injection and the other by bolus subcutaneous injection only) in addition to bolus glycopyrronium, suggesting that the first agent had not been successful. This will be explored further in examination of individual patients cases (Section 7.13). In Hospice 2, twelve (57%) patients received anticholinergics as a subcutaneous infusion via a syringe driver. The anticholinergic drug of first choice was hyoscine butylbromide and glycopyrronium was usually used as the second line agent.

Single bolus subcutaneous injection of glycopyrronium was not used as first line therapy in either hospice. Only one patient consented for the present study received glycopyrronium in the form of a 24-hour subcutaneous infusion.

7.9.2 Dose ranges of anticholinergic drugs used.

At Hospice 2 it was standard practice for doctors to routinely prescribe drug doses stating a range that could be administered. This practice was particularly common when prescribing subcutaneous infusions via the syringe driver and non regular ('as required' or 'prn') drugs . On administration the nursing staff would indicate the dose administered to the patient in the appropriate place on the drug administration record. This system required nursing staff to make a decision about the dose prescribed within the range indicated.

At Hospice 1, doctors did not routinely prescribe dose ranges. Doses were usually administered as prescribed with no decision on dosing required by the nursing staff. If an increase in dose was required, this was discussed with the prescriber and the drug administration record amended appropriately.

During the study period, it was observed that the dose range of hyoscine hydrobromide used at Hospice 1 was consistent; 0.4mg for a bolus subcutaneous injection and a starting dose of 1.2mg over 24 hours for a subcutaneous infusion. Two patients at Hospice 1 were prescribed bolus doses of hyoscine butylbromide (20mg and 40mg) or glycopyrronium (200 micrograms). The doses prescribed were consistent for glycopyrronium. One patient was prescribed hyoscine butylbromide by subcutaneous infusion (120mg over 24 hours).

At Hospice 2 however, the doses of anticholinergics administered, both for bolus subcutaneous injection and for a 24-hour subcutaneous infusion, showed more variation. The dose ranges prescribed and the doses administered to patients in the study at Hospice 2 are shown in Table 7.9.2.

differed in that the anticholinergic drug of choice for treating death rattle was hyoscine butylbromide which was administered subcutaneously as bolus doses and as 24-hour infusions. Nursing staff at Hospice 2 were also able to decide on the dose of drug to administer within a given range.

7.10 The use of noise level monitoring to assess the effect of anticholinergic drugs on death rattle.

7.10.1 Summary of the outcome of noise level monitoring at Hospice 1 and Hospice 2

As seen in Table 7.7.1, very few patients had both subjective and objective monitoring of the noise level of death rattle carried out. Furthermore, the quality of monitoring, in terms of regularity of recordings at the times stated in the protocol was poor. Only nine of the fourteen patients at Hospice 1 with some subjective data recorded also had some noise meter readings recorded. Noise meter readings in these cases were only present for all data points in two patients. A further seven patients had subjective noise scores recorded at Hospice 1 including some noise meter readings. Reasons for lack of data collection were sometimes documented on the study data collection sheet. Verbal feedback was also sought after each patient had been monitored. Nursing staff were sometimes reluctant to use the noise meter. The reason most commonly given for this was fear of causing, or exacerbating, anxiety within a patient's family.

A similar picture of noise recording was observed at Hospice 2. Again, "*issues with relatives*" being cited as the main reason given for not using noise meter evaluation. Noise meter readings corresponding to subjective noise scores were available for most of the data points in seven cases, but in three of these, there were three or fewer data points in total. Eleven patients with noise data recorded had incomplete noise meter readings taken.

7.10.2 Noise monitoring data and drug administration data collected for individual patient cases at Hospice 1 and Hospice 2

Data collected on drugs and interventions administered to patients and the monitored responses to these interventions were collated for each patient into a

series of tables and corresponding figures which can be found in Appendix I. Some individual cases will be discussed in more depth within the results to illustrate particular findings. All drug therapy administered in addition to anticholinergic drugs were recorded. Any particular issues regarding the consent procedure were noted plus any other relevant comments which might have affected the study results.

A primary aim of the present study was to determine whether a noise meter could be used to give a valid objective measure of death rattle. Previous studies had assessed death rattle subjectively. Secondary aims were to determine whether any differences could be detected in the treatment for death rattle. Owing to the complexity of treatment packages and delivery of treatment in the palliative care setting it is beneficial to examine individual patient cases in order to determine likely relevant factors that might influence therapeutic success.

7.10.3 Comparison of noise meter data with subjective noise scoring: validity of noise meter readings in the context of the present study.

The noise meter was used as an objective measurement of the volume of the death rattle. This was also assessed subjectively. A reduction in the noise level (either subjective or objective) was taken to indicate a positive measure of the effectiveness of the intervention to treat the death rattle. The results from the validation of the noise meter (Chapter 7 Part A) demonstrated, that under the specified conditions the meter should provide a valid outcome measure reflecting reduction in rattle noise. In order to confirm that this was also the case in the care environment of the present study, noise meter readings were compared with corresponding subjective noise scores where these were available from this study to see whether the noise meter provided a valid and reliable measure under the conditions of the study.

Inter-hospice comparisons were made in cases where both subjective and objective measurements of death rattle were available in order to determine if: a) the subjective scores correlated with the noise meter readings and b) whether

similar noise scores were associated with the same range of noise meter recordings in each Hospice. The results are shown in Table 7.10.3.

Table 7.10.3 Comparison of subjective noise scores with noise meter readings corresponding to those scores for Hospice 1 and Hospice 2.

Subjective Noise Score 0		Subjective Noise Score 1		Subjective Noise Score 2		Subjective Noise Score 3	
Noise meter readings (decibels) which corresponded to each subjective noise score							
Hospice1	Hospice 2	Hospice 1	Hospice 2	Hospice 1	Hospice 2	Hospice 1	Hospice 2
	40.7	41.8	44	49.1	43.3	47.8	49.6
	41	49	51	49.3	44	48.7	56
	41		52.5	50.1	46	52.2	60
	42		59.5	52.1	46	52.7	61.1
	42.5			52.5	46.4	53.3	
	45			53.5	46.5	53.4	
	47			55.5	48.6	53.6	
	48			55.5	49	54.6	
	53.1				50.2	55	
	53.8				51	55.3	
					51.3	56	
					52	56.7	
					53.2	56.8	
					56	57	
					57	59.3	
					63	65	
					63.1	66	
No paired data	Total 454.1	Total 90.8	Total 207	Total 417.6	Total 866.6	Total 943.4	Total 226.7
	Mean 45.4	Mean 45.4	Mean 51.75	Mean 52.2	Mean 50.97	Mean 55.49	Mean 56.67
	Range 13.1	Range 7.2	Range 15.5	Range 6.4	Range 19.8	Range 18.2	Range 11.5
	Standard deviation 4.95	Standard deviation 5.09	Standard deviation 6.36	Standard deviation 2.56	Standard deviation 5.96	Standard deviation 4.74	Standard deviation 5.20

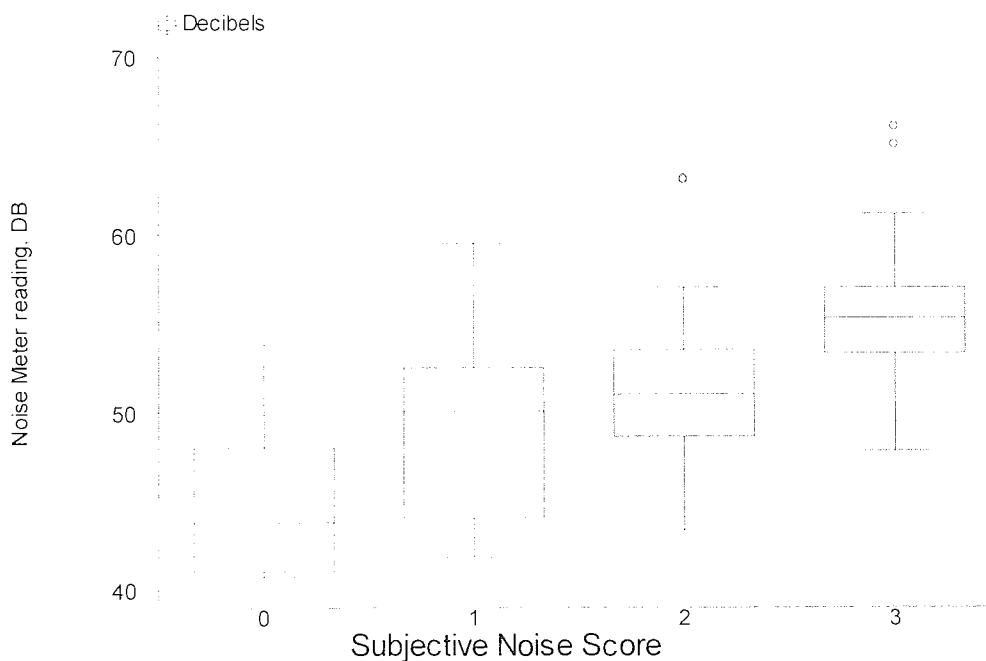
Key

Subjective Noise score 0= Inaudible, 1= audible only very close to the patient, 2= clearly audible at the end of the bed in a quiet room, 3= Clearly audible 20 feet from the bed in a quiet room.

From the raw data, the range of noise meter readings appeared as though the range of noise meter readings covered a similar range for both subjective scores of 2 and 3. There were no data to correlate to score 0 at Hospice 1.

Owing to the small amount of data, the noise meter readings were combined for hospices 1 and 2 to compare the range of noise meter readings with each of the subjective noise scores (0 to 3) as shown in Figure 7.10.3.

Figure 7.10.3 Box plot showing the spread of noise meter readings corresponding to the subjective noise scores for the combined data from both hospices



Using the Annova (F-test) which identifies whether there is a statistically significant difference between the four decibel means for each subjective noise score. There was a small correlation of subjective noise scores with the objective noise meter readings for the readings from the hospices when data was combined, which reaches statistical significance. The subjective noise scores therefore agree with the objective noise meter scores although there was some overlap observed with the data. The significance of these results is limited by sample size and that there were no data corresponding to 0 subjective noise score for Hospice 1.

Individual case profiles illustrated some particular anomalies with regard to the corresponding noise meter and subjective scoring. Patient case profile C004, (Appendix I) was subjectively scored at 3 for corresponding noise meter readings of 59.3, 53.6 and 47.8 decibels (dB). The noise meter indicated a gradual decrease in the volume of the death rattle whereas the subjective impression recorded was that of 'no change'.

A similar pattern was observed in patient case profile C006 (Appendix I). At the end of the period of monitoring, the subjective noise score for the death rattle was at 3, indicating loud rattle, with no change recorded throughout four data collection points, whereas the noise meter readings indicated fluctuating noise levels, diminishing at the last reading of the study period.

In addition to the subjective monitoring score and the objective noise meter monitoring, nursing staff were also asked to indicate whether they perceived that the noise death rattle noise had responded to the intervention by comparing the current noise score to the previous noise score, using the terms 'worse', 'the same', 'a little better', a 'lot better' as indicated on the data collection sheet (Appendix C).

Patient case profile C013 illustrated reported noise meter readings ranging from 49.1 to 52.1 decibels which corresponded to subjective noise scores of 2 and the descriptive markers of 'the same' or 'worse during the last four hours of life (Appendix I). A noise meter reading of 50 decibels corresponded to a comparative record of 'worse' although the numerical subjective noise score did not change from 2.

A better apparent correlation between subjective and objective noise scoring was illustrated by patient case profiles C009 and SM106 (Appendix I). Patient case profile C009 received only one bolus dose of hyoscine hydrobromide during the study period. The subjective noise score decreased from 3 to 2 then to 1 over 4.5 hours. The noise meter reading throughout the treatment was above 50 decibels although subjective score decreased to 1. No particular response was noted in the patient's medical records.

7.10.4 Duration of symptoms of death rattle prior to the patient being entered into the present study

The figures presented in Table 7.10.4 were collated from responses entered by the nursing staff on the data collection sheet (Appendix C). Most patients were reported to have been entered into the study within 6 hours of noisy breathing symptoms starting.

Table 7.10.4 Duration of symptoms of noisy breathing before entry into the study and subjective noise score just prior to death.

Length of time that death rattle symptoms were present prior to study entry	Length of time noisy breathing was present before entry into study		Number of patients with a subjective noise score of < 2 just prior to death		Number of patients with a subjective noise score > 2 just prior to death		Number of patients with unknown noise score just prior to death	
	Hospice 1	Hospice 2	Hospice 1	Hospice 2	Hospice 1	Hospice 2	Hospice 1	Hospice 2
<6 hours	7	10	1	1	5	7	1	2
<12 hours	2	3	2	0	0	1	0	2
<24 hours	1	5	2	2	0	1	0	2
Unknown	4	3	1	0	1	2	1	1
Total	14	21	6	3	6	11	2	7

If a subjective noise score of greater than 2 was taken as an indication of noisy breathing still being present just prior to death, this data indicated that for the majority of the patients for whom study data was available, good control of the death rattle noise was not achieved with the treatment given.

7.10.5 The timing of bolus subcutaneous doses of anticholinergic drug administered in relation to their apparent effectiveness and duration of effect on death rattle.

7.10.5.1 Response of death rattle noise to hyoscine hydrobromide injection

Patient case profiles, where there were at least two monitoring points within 60 minutes of an anticholinergic agent being administered, were analysed with regard to the percentage change, in either noise meter score in decibels (dB) or in subjective noise score which could be attributed to the intervention. The amount of data collected was too small to draw any statistically significant conclusions however the observations were important with regard to the validity and reliability of the outcome measures. Nine patients who received injections of hyoscine hydrobromide were observed to have a decrease in either subjective noise scores or noise meter readings (dB) within 45 minutes of administration of hyoscine hydrobromide. This decrease in noise scores was not always consistent in terms of time of onset, percentage reduction in noise score, or duration of action. Reduction in noise score were noted by a negative change and any increase in noise score by a positive change represented a rise in noise level as shown in Table 7.10.5.1.

Table 7.10.5.1 Patient case profiles where a change in one or both noise score levels (objective and subjective) was noted within 45 minutes of bolus subcutaneous administration of 400 micrograms Hyoscine hydrobromide or continuous infusion (C007 only).

Patient Case Profile (Appendix I)	Injection Number / Intervention	Time response recorded after injection (minutes)	Noise meter readings in decibels (dB)	Change in noise meter score in decibels (dB)	Subjective noise score (single number represents no change)
C002	3	45	No reading		2 to 1
C003	1	30	No reading		3 to 2
C004	1	30	59.3 – 53.6	-5.7	3
	1	60	53.6 – 47.8	-5.8	3
	2	50	No reading		2 to 1
	3 Repositioning Plus diamorphine 20mg	35	No reading		1 to 0
C005	1	35	66-65	-1	3
	1	105	65-53	-12	3
	2		No reading		
C006	1	30	No reading		3 to 0
	2 plus positioning	50	52.7-52.2	-0.5	3
	3 plus positioning	70	57-47.2	-9.8	3
C009	1	30	53.3-52.2	-1.1	3 to 2
	1	240	52.2 – 49	-3.2	2 to 1
C012	1	30	No reading		2 to 1
	1	60	No reading		1 to 0
	2	30	No reading		1 to 0
	3	35	55.5-50.1	-5.4	2 to 1
C015	1	45	45.9 – 44.2	-1.7	No reading
	1	135	44.2 – 43.5	-0.7	No reading
	1	245	43.5- 46.4	+2.9	No reading
	2	30	No reading		3
	2	150	No reading		3 to 2
	3		No reading		No reading
C007	Syringe driver 1.2mg plus position	30	No reading		2

Where noise meter readings were available, in five patients there was a reduction in noise score at 30 minutes after a bolus dose of 400 micrograms of hyoscine hydrobromide and further reduction after 70 to 100 minutes. No reduction was observed in the one patient profile (C007) where readings were available when a syringe driver of hyoscine hydrobromide was administered.

Interestingly, the decrease in noise meter readings, did not always correspond to a reduction in the subjective noise score given by the nursing staff. A further source of inconsistency was found when trying to interpret documentation regarding any response to interventions from the patient's medical records. For example, the individual patient case profile for patient C015 showed that nursing staff documented 'some relief' after the second injection of hyoscine hydrobromide, but no documentation of response was made resulting from the first injection, or documentation made on the data collection chart for subjective noise scores. In patient case profile C002, nurse documentation showed that hyoscine hydrobromide had been given with the result '*effective*' however the patient was described as '*still chesty*'. Later the patient was given glycopyrronium to see if it would be '*more effective than the hyoscine hydrobromide*'. Patient profile C007 only showed that following administration of hyoscine hydrobromide via the syringe driver, '*chest sounds clear*' was documented although no subjective or noise monitoring was carried out at the corresponding time. In the same patient, bolus hyoscine hydrobromide was prescribed 'as required' but none administered even though the last subjective noise score reported was 2.

7.10.5.2 Response of death rattle noise to hyoscine butylbromide injection

Where patient case profiles of those patients who received hyoscine butylbromide included at least two monitoring points within 60 minutes of an anticholinergic agent being administered, the change in subjective and objective noise scores were analysed. Results are shown in Table 7.10.5.2, again negative change represented by a negative sign and a rise in noise level by a positive sign.

Table 7.10.5.2 Patient case profiles where a change in one or both noise score levels was noted with syringe drivers (sd) and bolus subcutaneous administration of hyoscine butylbromide.

Patient Case Profile (Appendix I)	Injection Number / Intervention	Time response recorded after injection (minutes)	Noise meter score in decibels (dB)	Change in noise meter score (decibels)	Subjective noise score (single number represents no change)
C013	HBBr sd 120mg + HBBr bolus 40mg	110	No reading		2 to 1
	Sd + position	310 + sd	No reading		1 to 0
	HBBr bolus 40mg + sd	30	No reading		2
	HBBr 40mg bolus + sd	60	49.1- 49.3	+0.2	2
SM103	HBBr 40mg bolus (2 nd injection)	35	51-49	-2	2
SM105	HBBr sd 120mg (+ GLY bolus)	495	56		3
SM106	HBBr bolus 40mg	210	52.5-51	-1.5	1
		350	51-57	+ 6	1 to 2
SM107	HBBr sd 80mg	1095	41 to 53	Fluctuating	0
	HBBr sd 120mg	1440	41 to 42, 53.1	Fluctuating	0,2,0
	HBBr bolus 40mg +sd	30	46-44	-2	2
	HBBr bolus 40mg +sd	No reading			2
	HBBr bolus 40mg + sd	No reading			2
SM108	HBBr bolus 40mg (+ HBBr sd 120mg)	60	No reading		3
SM115	HBBr bolus 20mg	45	56.7- 61.1	+4.4	2 to 3
	HBBr bolus 20mg +sd 120mg +diamorphine/midazolam sd	45	61.1 – 43.3	-17.8	3 to 2
SM117	HBBr sd 120mg	45	No reading		2
	HBBrSd 120mg	105	No reading		2
	HBBrSd 120mg	365	No reading		2
	HBBr 40mg + HBBr sd 120mg	30	No reading		3
SM118	HBBr sd 120mg + HBBr bolus 40mg	25	No reading		2
		360	No reading		2 to 1
SM121	HHBr bolus 40mg + (HBBr sd 80mg)	170	No reading		2
	Suction + HBBr sd 80mg		No reading		2

Key:

HBBr = hyoscine butylbromide
GLY = glycopyrronium

sd = syringe driver
HHBr = hyoscine hydrobromide

Where data was available from patient case profiles where hyoscine butylbromide was administered, only three patients received bolus injections of hyoscine butylbromide alone, SM103, SM106 and SM115 which resulted in a change in noise score. Patient case profile SM103 showed a reduction in noise meter score 35 minutes after a bolus injection of 40mg hyoscine butylbromide and patient case profile SM106 demonstrated a reduction in noise meter reading 210 minutes after the injection of 40mg hyoscine butylbromide. The long time delay before the response to the injection was recorded was owing to the lack of a baseline noise level. The first noise level was taken 50 minutes after the bolus injection of hyoscine butylbromide (Appendix I).

Patient case profile C013 showed an initial response to the syringe driver of hyoscine butylbromide and first bolus injection of 40mg hyoscine butylbromide according to the subjective score. However the overall profile was one of rattle not being relieved. (Diamorphine, levomepromazine and midazolam were administered concomitantly.) The death rattle noise recorded for patient case profile SM106 rose again after nearly 6 hours but no further anticholinergics were given, perhaps as the patient was in a single room and unlikely to disturb other patients. The case profile for Patient SM103 showed that they continued to have subcutaneous fluids and breathing noted to be '*laboured and bubbly*' (Appendix I).

The Patient case profile SM115 did not demonstrate a response to 20mg hyoscine butylbromide and the noise level increased, as indicated by both a rise in the noise meter reading and by subjective noise scoring. A reduction in noise level was recorded after the second injection of hyoscine butylbromide which was given concurrently with 120mg hyoscine butylbromide in the syringe driver over 24 hours with diamorphine and midazolam. The noise of a relative talking was noted to have possibly interfered with what was considered a high noise meter reading. Relatives attending this patient were noted to be present and distressed, the patient was cared for in a multi-bedded bay (Appendix I).

The Patient case profile SM107 showed a variable response to an infusion of hyoscine hydrobromide 120mg, showing first an increase in noise level and then a gradual decline. The noise level rose again and a reduction in noise level was seen 30 minutes after an additional bolus injection of 40mg hyoscine butylbromide. Subjective noise levels remained at 2 and no response was indicated to further bolus injections of hyoscine butylbromide. The possibility of soup aspiration was noted in this patient, who was still taking oral medication and the noise level was noted to reduce after coughing, rather than being related to medication. Both medical and nursing notes recorded that the patient did not appear to be distressed by the rattling (Appendix I).

The Patient case profile SM118 did show a reduction in noise level 6 hours after a bolus dose of hyoscine butylbromide in addition to the syringe driver administering 120mg hyoscine butylbromide over 24 hours. This patient was monitored for the longest period of time, however the timing of noise recording was not always as required by the study protocol. This patient's medical records indicated that the patient may have had pneumonia and that position change seemed to resolve some of the 'chestiness' (Appendix I).

The remaining patients did not appear to have a reduction in rattle noise in response to hyoscine butylbromide. Patient case profile SM105 noted that the patient was '*chesty on admission*' and noted to have '*thick and lumpy secretions*'. Two syringe drivers had been in situ for a long period of time, one containing diamorphine together with hyoscine butylbromide 120mg and the other containing ketamine and midazolam. The Patient case profile SM108 showed that the patient also had shortness of breath on admission and was receiving oxygen, and reported to be short of breath when lying flat. The Patient case profile SM121 showed that suction was performed for this patient, apparently with some effect, however subjective noise scores remained at 2 throughout the monitoring period. The Patient case profile SM103 showed a response to the second injection of hyoscine hydrobromide indicated by the noise meter, however subjective scoring remained the same, at 2. Subcutaneous fluids were continued in this patient. Finally Patient case profile SM117 was noted to be short of breath on admission

and required continuous oxygen. Agitation was noted to be the principle problem for this patient (Appendix I).

7.10.5.3 Response of death rattle noise to glycopyrronium bromide injection

Data was available from six patients who received glycopyrronium injection which was used in the present analysis. In contrast to hyoscine hydrobromide and butylbromide, glycopyrronium was generally administered after other anticholinergic drugs had been used. An exception was demonstrated in Patient case profile C011 where glycopyrronium was administered at the same time as treatment with a subcutaneous infusion of hyoscine hydrobromide. The responses are shown in Table 7.10.5.3.

Table 7.10.5.3 Patient case profiles where a change in one or both noise score levels was noted following a bolus subcutaneous administration of glycopyrronium

Patient Case Profile (Appendix I)	Injection Number / Intervention	Time response recorded after injection (minutes)	Noise meter score in decibels (dB)	Change in noise meter score (decibels)	Subjective noise score (single number represents no change)
C011	HBr sd 1.2mg + 3 GLY bolus 400mcg	73	56-56.7	+0.7	3
	3 GLY bolus 400mcg	103	56.7-55.3	-1.4	3
	3 GLY bolus 400mcg	163	55.3-56.8	+1.5	3
C013	5 GLY bolus 400mcg + HBr 120mg sd	30	55.5-55.2	-0.3	2
SM105	3 GLY bolus 400mcg + HBr 120mg sd	30	56-60	+4	3
SM117	HBr sd 120mg + 2 GLY bolus 800mcg	30	No reading		3
	2	240	No reading		3
	3 GLY bolus 400mcg	30	No reading		3
	3	125	No reading		3
	4 GLY bolus 400mcg	30	No reading		3
SM118	3 GLY bolus 800mcg + HBr 120mg sd	200	No reading		2 to 0
SM121	2 GLY bolus 00mcg + HBr 80mg sd	80	48.6 – 51.3	+2.7	3

Key

HBr = hyoscine butylbromide HBr = hyoscine hydrobromide sd = syringe driver
 GLY = glycopyrronium

Only one patient case profile, SM118, demonstrated a positive response to glycopyrronium injection. Glycopyrronium was given in addition to an infusion of hyoscine butylbromide via a syringe driver and this patient had experienced a fluctuating pattern of death rattle noise level throughout the study period. None of the other patients in this group showed any significant response to glycopyrronium either via the noise meter reading or subjective noise monitoring. It should however be noted that all of these patients had received glycopyrronium

because they had death rattle which had appeared resistant to the usual anticholinergic regimen and all bolus glycopyrronium injections were in addition to the background syringe driver which contained hyoscine butylbromide in all patients except C011 where hyoscine hydrobromide was infused (Appendix I).

Additional comments in the nursing and medical notes made in the patients medical records and recorded in the patient case profiles (Appendix I) indicated other factors which may have affected the course of the death rattle symptom. Patient C011 had been noted to have a history of recent chest infection and twelve hours before entry to the present study their respiratory tract secretions were noted to be increased. Patient C013 had death rattle symptoms which seemed resistant to all interventions. Patient SM105 had needed physiotherapy to assist expectoration, on admission to the hospice, and secretions were noted to be *'thick and lumpy'*. For this patient, nursing notes recorded most improvement from suctioning. Patient SM121 also had suction performed, an indication that secretions were a particular problem. Finally, an effect of glycopyrronium on death rattle may have occurred in patient SM118, 3.5 hours after administration, however the overall picture of rattling seemed to fluctuate from day to day and this patient may have had pneumonia (Appendix I).

7.11 Time intervals between administration of anticholinergic drugs

An analysis of the period of time between bolus subcutaneous injections of anticholinergics in relation to their apparent duration of effect in relieving death rattle was carried out from the patient case profiles. Data was collated from the data collection chart, timing of drug administration from the drug administration chart and information recorded in the patients medical records. The time between bolus injections of hyoscine hydrobromide is shown in Table 7.11.1. Consecutive noise monitoring data was not available for Patient case profile C010 although eight bolus injections of hyoscine hydrobromide were administered. The nursing staff recorded this patient to have *'noisy respirations'*, but to be *'comfortable throughout'* also that he *'remained poorly and breathless'*. *'Some benefit'* from the hyoscine hydrobromide injections were noted (Appendix I).

Table 7.11.1 Time interval between bolus injections of hyoscine hydrobromide 400 micrograms

Patient Case Profile No. (Appendix I)	Injection number (Numbered consecutively in time as administered in Appendix I)	Time interval between injections/hours and minutes
C004	1 and 2	44 hours
	2 and 3	38 hours
C005	1 and 2	4 hours 15 minutes
C006	1 and 2	45 hours 30 minutes
	2 and 3	11 hours 50 minutes
C010	1 and 2	2 hour 55 minutes
	2 and 3	5 hours
	3 and 4	13 hours 55 minutes
	4 and 5	9 hours 35 minutes
	5 and 6	4 hours 25 minutes
	6 and 7	6 hours 51 minutes
	7 and 8	6 hours 30 minutes
C012	1 and 2	28 hours and 30 minutes
	2 and 3	38 hours

As the hyoscine hydrobromide injections were prescribed 'as required' (prn) allowing the nursing staff to administer when needed, it would seem reasonable to assume that further doses were given when symptoms were thought to warrant further intervention. There were large inter-individual and intra-individual variations in the time between administration of injections of hyoscine hydrobromide. The mean time between administration was 18.55 hours with a standard error of the mean (SEM) 16.35 hours. The time between bolus injections may therefore have been taken to represent the duration of action of the anticholinergic agent.

Any duration of effect resulting from single injections of hyoscine butylbromide or glycopyrronium was difficult to estimate as most patients had concurrent infusions of other anticholinergic agents. In addition, the act of prescribing or administering

glycopyrronium to this group of patients reflected death rattle symptoms that were particularly resistant to treatment.

In addition to the data recorded on the monitoring chart, it was noted that occasionally other interventions were carried out and noted by nursing staff in the patients medical records notes but not recorded on the study data collection chart such as '*patient turned*', '*nursed on 30 degree tilt*'. Sometimes these occurred at the same time that the anticholinergic injections were administered, the nursing staff often taking the opportunity to alter the patient's position if necessary at the same time as giving the injection. This practice made it very difficult to assess the outcomes of two or three different interventions. This was demonstrated by the Patient case profile C006 (Appendix I) where a change of position was documented at each noise level measurement, coinciding with administration of hyoscine hydrobromide. The complexity of factors involved in trying to identify the significant therapeutic intervention will be explored further in Section 7.14.6.2.

7.12 Evidence of underlying respiratory infection or other underlying condition predisposing to death rattle on entry to this study.

Nursing staff were asked to record on the data collection form whether patients had been observed to have any sputum production prior to or on entry to the present study. The results are shown in Table 7.12.1.

Table 7.12.1 Patients observed to have evidence of increased sputum production prior to, or on entry to this study.

Green or yellow sputum recorded	Hospice 1	Hospice 2
Yes	1	2
No	8	14
Don't know	5	1
Not recorded	0	4

This question was included on the data collection sheet in order that patients with a possible infectious aetiology for their death rattle could be identified. In addition to information collected on the data collection form, additional information was also extracted from the patient's drug administration cards and medical records (Table 7.12.2). Nine of the study patients (26%) were considered to have a possible increased risk of underlying respiratory infection, as indicated from the medical records and drug administration chart .

Table 7.12.2 Relevant past medical history which may be factors in development of noisy breathing in those patients monitored

Past medical history	Number of patients monitored with additional potential risk factors for developing death rattle
Possible evidence of recent or underlying respiratory infection	9
Concurrent administration of subcutaneous fluids	4
Past history of Asthma or COPD	2
Pleural effusion	1
Ascites	2
Left ventricular failure	1
Ischaemic heart disease	1
Renal failure	1
Long period in the study, (prolonged dying phase)	1

Comments in the medical records such as '*chesty, required physiotherapy*' on admission together with previous oral or intravenous antibiotic therapy in the

weeks preceding admission, were thought to indicate the possibility of an increased risk of an infective origin or aspect to the death rattle. Patients case profile considered to indicate this risk were: C011, C005, C012, C010, C003, SM105, SM107, SM108, and SM113 (Appendix I). All of these patients had noisy breathing symptoms which persisted in spite of treatment with subcutaneous infusions plus bolus injections of anticholinergics. Unfortunately the quality of noise level monitoring was compromised for different reasons in some of the cases: Patient case profile C003 recorded subjective noise scoring only; Patient case profile C010 included evidence from the medical records that noisy breathing was present just before death occurred, although noise monitoring was stopped at the relative's request. The case profile of patient SM107 recorded a long study period of 13 days, which could be described as a prolonged dying phase (Appendix I).

Only three of this group of nine patient case profiles were identified as having green or yellow sputum at entry to the study; C002, SM105 and SM107 all of whom continued to have noisy breathing until death or last recorded noise score (Appendix I).

Patient case profile C002 was identified as having yellow sputum on the data collection chart at study entry. Although this patient was in the study for four days, there were only two data points recorded. However evidence from the drug administration chart showed that bolus subcutaneous injections of hyoscine hydrobromide were required regularly and glycopyrronium was administered *"to see if it was any more effective than hyoscine hydrobromide"*, implying that the hyoscine hydrobromide had not been effective (Appendix I).

'Beige sputum' was recorded at study entry for Patient case profile SM105 (Appendix I). Data recording was poor with only two noise meter recordings and three subjective noise monitoring points over the two days of the study. The drug administration chart indicated that the administration of hyoscine butylbromide via the syringe driver had not been completely effective, as bolus injections of

glycopyrronium were given in addition. Nursing staff finally performed suction on this patient to which little response was noted.

Patient SM107 was noted to have significant sputum present at the start of the study. A pattern of fluctuating noise level was apparent from the noise meter readings during the study, which continued until death. Death rattle symptoms were not responsive to hyoscine butylbromide via the syringe driver over a period of eight days or to additional bolus injections of hyoscine butylbromide administered in the last 48 hours of life. Information taken from the patient's medical records indicated the presence of recent previous chest infection.

In addition to these three patients, other patients who exhibited persistent death rattle had been noted to be '*chesty*' in the medical notes and were prescribed concomitant respiratory medication such as inhaled bronchodilators, cough medication and oxygen. The following patient's case profiles fell into this category and had persistent death rattle symptoms: SM115; SM113; SM108; SM117 and SM114 (Appendix I).

Patients with other underlying conditions which might predispose to the development of death rattle were noted but numbers were not felt to be large enough to make significant comment.

7.13 The comparative efficacy of anticholinergic drugs to treat death rattle symptoms

In order to assess whether the anticholinergic treatment had been successful in achieving control of noisy breathing, and to determine if there were any trends in outcome, an analysis was carried out of the responses of patients treated with subcutaneous infusion of anticholinergic drugs, compared to those given subcutaneous bolus injections. Data from the objective and subjective noise monitoring, together with information from the drug administration charts and medical notes were used (Appendix I). The first group compared, were those receiving bolus subcutaneous injections of anticholinergics and are shown in Table 7.13.1.

The responses of noisy breathing were divided into four categories

- a) Those patients with an **initial response** that is, a reduction in death rattle was seen following the first treatment intervention with anticholinergics
- b) A **fluctuating picture** of response with no particular trend of response observed with time in relation to drug interventions.
- c) An **overall satisfactory response** where noisy breathing was noted to have reduced in noise level after treatment with anticholinergic drugs, together with documented relief of symptoms in the patient's medical records.
- d) An **unsatisfactory response** to interventions to noisy breathing overall, with continuing intervention and little reduction in noise score together with supporting documentation recorded in the patient's medical records.

For the purposes of this analysis, in the absence of an accepted published definition, a satisfactory response was defined as a reduction in noise level to a subjective score of 1 (audible only very close to the patient) or less, in response to an intervention, with no requirement for frequent administration of bolus doses of equivalent or increasing doses of anticholinergic drugs, together with additional evidence from patient medical records. Ideally this response should be maintained for a large proportion of the dying phase, however it was not considered that the data collected from the present study could accurately represent this element. An unsatisfactory response was defined as no or little response to interventions for the treatment of death rattle as indicated by no or short lived reduction in noise score together with additional supporting evidence from patient's medical records.

Table 7.13.1 Overall responses of death rattle symptoms to bolus subcutaneous injections of anticholinergic agents.

Response to bolus subcutaneous injections of anticholinergic drugs	Patient case profile number (Appendix I)
Initial response	C003
	C006
	C008
	C009
	SM104
	SM110
Fluctuating picture	C004
	C012
	C015
	SM103
Overall satisfactory response	C002
	SM108
	SM104
Overall unsatisfactory response	C011
	C005
	SM106

The second group compared were those patients receiving continuous infusion of anticholinergic drugs (Table 7.13.2.) The following patient case profiles where anticholinergic drugs were administered by infusion via a syringe driver could not be categorised into any of these groups: Patient case profile SM101, initially showed no response in the noise level of death rattle after initiation of the syringe driver. A reduction in noise level was then later recorded in response to an increased dose of anticholinergic drug, subcutaneous fluids were given but no further bolus doses of anticholinergics. Patient case profiles SM111, SM113,

SM116 and C010 did not have enough readings taken to make an assessment of efficacy of treatment (Appendix I).

Table 7.13.2 Overall responses for noisy breathing for patients to whom anticholinergics were administered by continuous subcutaneous infusion via a syringe driver

Response to continuous subcutaneous infusions of anticholinergic drugs	Patient case profile number (Appendix I)
Initial Response	C013
	SM102
	SM112
	SM120
Fluctuating response	SM101
	SM102
	SM107
	SM112
	SM118
Overall satisfactory response	SM101
	SM114
Overall unsatisfactory response	C013
	C011
	C007
	SM105
	SM108
	SM121
	SM120
	SM117
	SM115
	SM112

There are acknowledged limitations to this process of analysis and categorisation, which is very subjective. There is also the confounding factor that subcutaneous infusions in the present study usually administered hyoscine butylbromide, apart from Patient case profiles C011 and C007 where infusions of hyoscine hydrobromide were administered (Appendix I).

Using this analysis however, ten of the monitored cases in the present study treated mainly with infusions via a syringe driver and three of those treated mainly with bolus injections of anticholinergics were classified as not achieving a final overall response in reduction of death rattle noise.

7.14 Concomitant medication received by patients during the monitoring period.

A record of all other drugs administered to patients during the study period was taken from the patient's drug administration chart. Details were recorded in the patient case profiles (Appendix I). The most common medications administered to patients in the present study in addition to anticholinergic agents are shown in Table 7.14.1. Continuous subcutaneous infusions and bolus subcutaneous injections of diamorphine and midazolam were prescribed most often. Other medication administered to patients which are not included in Table 7.14.1 were ; methadone subcutaneous infusion (1 patient), metoclopramide infusion (1 patient), dexamethasone subcutaneous infusion (2 patients), and bolus injection (2 patients), ketamine subcutaneous infusion (1 patient), oral morphine (2 patients), oral oxycodone (1 patient), cyclizine subcutaneous infusion (1 patient), ketoprofen subcutaneous infusion (1 patient) and codeine linctus (1 patient). By this stage in the patients illness most oral medication had been stopped and although oral pain medication was prescribed when required, for breakthrough pain. In addition nebulised salbutamol was administered to four patients and nebulised saline to one patient.

Table 7.14.1 Drugs most commonly administered to patients in the present study in addition to anticholinergic agents

Drug	Number of patients in Hospice 1 (n=14)	Number of patients in Hospice 2 (n=21)	Total (n=35)
Diamorphine subcutaneous infusion	7 (50%)	18 (86%)	25 (71%)
Diamorphine subcutaneous bolus	6 (43%)	6 (29%)	12 (34%)
Midazolam subcutaneous infusion	9 (64%)	14 (66%)	23 (66%)
Midazolam subcutaneous bolus	5 (46%)	12(57%)	17 (48%)
Levomepromazine subcutaneous infusion	3 (21%)	3 (14%)	6 (17%)
Haloperidol subcutaneous infusion	0	2 (9%)	2 (6%)
Hydromorphone subcutaneous infusion	2 (14%)	0	2 (6%)
Clonazepam subcutaneous infusion	0	3 (14%)	3 (9%)
Clonazepam subcutaneous bolus	0	4 (19%)	4 (11%)

Some of these drugs would be administered combined in a syringe driver, most notably diamorphine and midazolam. Other agents would be administered separately owing to drug compatibility issues. Occasionally drugs were combined even though compatibility was not assured.

Data from the drug administration charts indicated that the concomitant administration of bolus injections of diamorphine and midazolam with anticholinergic agents occurred in some patients but not as frequently as had been expected and did not often coincide with monitoring of the noise level data. Where it was apparent from the timing on the drug administration chart that this had occurred, on the patients where closer analysis was done, this was noted in the patient case profile. It was more common for patients to require 'top-up' bolus injections against a background of infused drug therapy. The background infusions administered for the symptom control were assumed, for the purposes of the analysis to be constant, having minimal effect on the outcome of the acute administration of a bolus dose of anticholinergic for the treatment of death rattle. A more frequent confounding factor was that the patient was often repositioned at

the time of administering anticholinergics, making the assumption that any response was due to the anticholinergic drug unreliable.

Most of the concomitant medication was administered with the main aim of symptom control of pain, nausea, agitation and to prevent fitting. Oxygen was usually administered to support underlying respiratory conditions and oxygen therapy was generally initiated before hospice admission. Oxygen was administered to three patients in the study, one at Hospice 1 and 2 at Hospice 2.

Although the use of diamorphine and midazolam was common practice between the two hospices, certain elements of drug use were different. Subcutaneous methadone infusion via the syringe driver would occasionally be used at Hospice 1 where as subcutaneous ketamine infusion would be used at Hospice 2, both alternative agents were used to treat pain unresponsive to routine opioid agents. Subcutaneous hydromorphone infusion was only used in Hospice 1 in this study and clonazepam was only used at Hospice 2.

7.15 Adverse Effects of anticholinergic agents noted during the study

Very few patients had any data recorded on the adverse effects section of the data collection form (Appendix C). Five patients at Hospice 2 were recorded as having a dry mouth and thick secretions. No adverse effects were recorded on the data collection chart in Hospice 1. Review of the patient's medical records however revealed that patients may have experienced adverse effects which could possibly have been attributed to treatment with anticholinergic agents and yet were not recorded on the data collection form. (This is not equivocal evidence however, as this is anecdotal data and symptoms may have been due to underlying disease). Nursing staff may not have associated adverse effects with the anticholinergic treatment, or may have merely forgotten to complete the data collection tool. No indication of a connection between such adverse effects and anticholinergic therapy was made in the patient's medical records.

The following patients had effects that may have been associated with anticholinergic treatment: The patient case profiles C011, C012, C007, SM110 (Appendix I) recorded evidence of urinary retention, either as the patient having not passed urine for over 24 hours or that the patient required catheterisation. Sometimes however it was noted that only a minimal amount of concentrated urine was passed, indicating the possibility of dehydration or renal involvement. One Patient case profile, C006, recorded the patient as '*being thirsty*'. This could have been a side effect of anticholinergics or a symptom of dehydration. Patients SM105, C018 were noted to have '*thick tenacious sputum*' and '*thick and lumpy secretions*'. The Patient case profile SM121 noted the patient to have a '*dry mouth but with chest secretions*' (Appendix I). The dry mouth may have been a symptom of the anticholinergic treatment, and presence of chest secretions indicating lack of response to treatment.

7.16 Discussion

7.16.1 Overall hospice data.

At the time that the present study was started, no previous investigation had used a randomised controlled methodology or compared the outcome of treatment in more than one hospice observing their normal practice in the treatment of death rattle. In contrast to some studies (Back et al, 2001; Hughes et al, 2000) neither medical or nursing staff worked at both hospices in the present study, and this may have indirectly had a bearing on practice. However although no written protocols existed for the treatment of death rattle in either of the hospices, observed practice during the present study was representative of normal practise. The origin of each hospice's practice in the treatment of death rattle was influenced by previous and current medical practitioners practice, which did not appear to vary greatly during the study period. The only exception to this was a Specialist Registrar working at Hospice 1 for six months during the study period who prescribed hyoscine butylbromide in preference to hyoscine hydrobromide, which was a deviation from normal practice. The use of prescribing ranges, allowing nursing staff a degree of discretion in the dose administration process in Hospice 2, together with a smaller ratio of medical to nursing staff, may have had

an effect on the doses administered at that hospice both for subcutaneous infusions and 'as required' drugs.

Differences existed in the relationship of the author to the two Hospices, being based and working clinically at Hospice 1. During the study there was increased contact with Hospice 2 through attendance at weekly ward round meetings and as a result of study monitoring, resulting in a more even exposure to staff at both Hospices.

7.16.2 Comparison of hospice demographic data

Hospices were required to collect certain statistics for submission to the Healthcare Commission and to provide a minimum data set. However the data collection methods were not standardised and databases differed from one hospice to another.

Although the data collection periods in the present study were not of equal duration, the number of inpatient admissions (from the admission data collected from the hospice database) showed a difference of only 10 patients. This would be accounted for by the larger number of beds at Hospice 2 allowing more patients to be admitted. The number of in-patient deaths occurring during this time were similar and generally representative of both institutions (Poulson K, 2005; Castenhiera P, 2005).

The average lengths of stay were also representative for each institution. Occasionally one or two patients staying in the hospice for a longer than average period of time skews the overall mean stay length. This was true for the Hospice 1 length of stay during the study period. Overall, the population age spread was comparable between the study sites. Data was collected from the database for each Hospice. Although comparative standard data sets for some data were collected, the computerised management systems for each hospice were different and therefore may have resulted in minor differences in the way in which data was entered, particularly with regard to primary diagnosis. Hospice 2 seemed to have a higher proportion of buccal cavity and pharyngeal tumours. This may be accounted for by the fact that the hospice was situated close to a

teaching hospital with a large Ear Nose and Throat department, a similar situation was true for haematological malignancies and neurological conditions.

7.16.3 The number of patients consented for entry into this study

The study data showed a low percentage of the patient admissions (Hospice 1, 7.6% and Hospice 2, 8.7%) and subsequent deaths (Hospice 1, 10.6% and Hospice 2, 17%) in each hospice being consented for entry into the present study.

Reasons given for this by the medical and nursing staff involved in these aspects of the study were varied, but were influenced by personal and cultural issues. A comment made by one of the admitting doctors with regard to obtaining consent was that it was difficult to ensure an understanding in patients that this study was examining the effect of current therapy, rather than investigating a new treatment. Another perceived barrier to obtaining consent, identified by the same doctor, was the requirement for the patient to sign the consent form at multiple points. The need for multiple signatures was considered to imply an importance to the consent form out of proportion to the significance for which it was intended, particularly as the present study was observing current therapy rather than a new experimental treatment. A comparison was made with the fact that patients were only required to give verbal consent for a doctor to give treatment with acupuncture whereas the present study methodology was non-interventional. Opinion was expressed that the burden of making a decision about consent for this study was too great for the patient at this period in their life. The result of this procedure was that bias would be introduced into the present study as patients might be selected on the doctor's assessment of their ability to undertake the consent procedure. For example attitudes were expressed such as *'This is an anxious patient and we do not want to add to her anxiety'*. This standpoint would bias towards selection of patients who were *'articulate and emotionally stable'*. The perception was expressed that many patients and relatives are anxious about being admitted to the hospice, with the associated terminal nature of their

illness and that to ask for consent to any study at this time would place additional burden on them.

Another issue which affected the consent procedure in the present study was motivation and whether entry into the study was at the forefront the doctor's plan of treatment for the patient. External factors such as the time of day of the patient's admission, how many staff were available, other pressures such as meetings and other external emotional pressures arising from the hospice environment, could affect whether the doctor chose to obtain consent from a patient. Often the discussion of death rattle might not be felt appropriate to address with the patient at all, and would be addressed with relatives if and when the symptom occurred, in an attempt to cause less of a burden of anxiety on the patient or relative. Many of these issues surrounding attrition in palliative care research were reported by Grande and Todd (2000).

Rees and Hardy (2003) addressed consent in palliative care patients by investigating the acceptability of the consent process in an ongoing randomised controlled trial between hyoscine and glycopyrronium in the treatment of death rattle. All patients admitted to palliative care wards in a major teaching hospital were given an information sheet explaining that research was an integral part of patient care. The information sheet detailed all of the study types taking part on the unit and advised that patients may be approached for consent to studies during their admission. The authors concluded that this process could still be subject to selection bias. The proposed method of patient recruitment in Rees and Hardy's study (2003) was similar to those expressed in the present study, as trial suitability was determined at pre-round multidisciplinary meetings. Patients too unwell, unable to understand English or likely to be distressed were not approached. Rees and Hardy's (2003) consent procedure contained a standard requirement to sign a form. Patients were not randomised until the symptom of noisy breathing developed. If patients were subsequently discharged then re-admitted, they would be asked to re-sign consent forms.

Rees and Hardy's (2003) work was carried out in a large teaching hospital within a culture where staff were supported and encouraged to work in an environment of active research. Patients nursed on the palliative care wards in a teaching hospital environment are likely to have been exposed to and be familiar with the culture of clinical trials within the oncology department. It is very likely also that the consenting consultant had personal motivation to recruit patients for the study. Barriers to consenting patients in the present study were identified to be lack of personal motivation within the hospices, including no direct ownership of the research project, apart from the author. Motivation of nursing staff was variable, even though when questioned directly, the support for the present study from the nursing and medical staff was enthusiastic. There may be an underlying culture in the hospices against the idea of carrying out research in this group of patients, in contrast to the culture referred to in a large teaching hospital. There were also issues of emotional sensitivity and a perception that the present study was asking nursing staff to do something which conflicted with what they perceived as their impartial caring roles.

Over 6 months Rees and Hardy (2003) followed their consent procedure and considered 107 patients for entry to their study comparing glycopyrronium bromide with hyoscine hydrobromide for the treatment of death rattle. Of these, 58 (58.4%) patients were consented and entered into the study, 34 patients declined and 15 proved unable to be randomised, 12 patients were still alive leaving fifteen patients who had been randomised to receive study treatments. It is not possible to compare initial consent data from this study as the criteria for comparison of the consented population were not defined, however the final number of patients randomised for treatment in Rees and Hardy's (2003) study was 25% of those consented at that time. The percentage of patients who were given anticholinergics and monitored as a percentage of those consented in the present study were 51% at Hospice 1 and 40% at Hospice 2. One of the disadvantages of pre-consenting is that patient's are consented and are then 'lost' to the study. This only happened to one patient in the present study, who was admitted to a local hospital. Two patients were not consented into the study at the request of their relatives.

Although at the start of the study there had been an intention to approach all patients who were admitted to the hospice for expected terminal care, in practise this did not happen, for the reasons given above. There was not an existing established research culture in Hospice 1 or Hospice 2 (or indeed within any of the West Midlands hospices) which made obtaining patient consent for the present study more difficult.

The location of Hospices and close system of working across the West Midlands could however provide an ideal opportunity for multicentre research and provide significant numbers of patients to be recruited for a randomised controlled trial.

Conducting the present study in just two centres required both continuous and considerable encouragement (by the author) of the medical and nursing staff to consent and recruit patients for monitoring. It would not have been practical to recruit further centres to increase numbers without an influential lead clinician in each hospice or a funding source to secure dedicated time of a research assistant.

In total 76 patients were consented into the present study at the two hospices, from a possible total of 571 in-patient deaths. Compared with other prospective observational studies of death rattle, the present study did not recruit as many patients (Table 5.1.1 and 5.1.2), however consent was only mentioned as part of the methodology of one of the studies (Ellershaw et al, 1995) where 82 patients were recruited. It is not clear whether verbal or written consent was sought. The consent procedure, is considered to have had a significant effect on reducing the number of patients recruited into the present study.

The percentage of patients who were administered anticholinergics for death rattle, including those identified who were not consented into the present study was 35% at Hospice 1 and 44% at Hospice 2, which is similar to incidences quoted in other studies (Section 2.2).

7.16.4 Length of time that symptoms were present before treatment with anticholinergics was started in relation to noise scores during treatment.

It has been suggested that the early use of anticholinergic agents in relation to the start of symptoms would lead to more effective treatment of death rattle based on the hypothesis that it is necessary to prevent the build up of secretions (Power and Kearney, 1992). Most of the patients were entered into the present study within 6 hours of noisy breathing being noted. No trend was seen for lower noise scores in this group of patients. Patients whose death rattle symptoms had been present for longer than 6 hours before entry into the present study did not show any trend toward noise scores greater than 2 just before death. Obviously the numbers involved in the present study are small but do not support the hypothesis that early treatment with anticholinergic drugs is more effective in reducing death rattle symptoms. Noise scores were not compared to length of stay, as patients may have been admitted acutely from home, where it is not known exactly how long symptoms may have been present before treatment.

7.16.5 Choice of anticholinergic regimen at each Hospice

Hyoscine butylbromide had traditionally been the standard anticholinergic agent used for respiratory tract secretions at Hospice 2 for several years, following an in-house survey of hyoscine use and based on cost effectiveness data (Bausewein and Twycross, 1995). Hospice 1 preferred a first line approach of hyoscine hydrobromide bolus injections. Hospice 2 tended to administer anticholinergics via subcutaneous infusion more often than Hospice 1. Neither hospice used glycopyrronium first line, and tended to reserve it as a last resort, when all other treatment had failed. Several recent publications have suggested that glycopyrronium bromide may be a cost effective alternative to hyoscine hydrobromide (Murtagh et al, 2002; Bennett et al, 2002) however use of glycopyrronium was not common first-line treatment in West Midlands Hospices at the time the present study was conducted.

7.16.6 Dose ranges of anticholinergic drugs use

7.16.6.1 Variation in doses of anticholinergics used at each hospice at initiation of treatment or during treatment

The results in Tables 7.9.1 and 7.9.2 show the wide range of doses of the three different anticholinergics prescribed within the hospices.

No treatment specific local protocols or guidelines for prescribing anticholinergic agents were in place in either of the two hospices in the study. The prescribing pattern at Hospice 1 was however more consistent than Hospice 2 with regard to doses and choice of anticholinergics administered. Hyoscine hydrobromide tended to be the usual anticholinergic prescribed, in a dose of 0.4mg for bolus injection and 1.2mg for subcutaneous infusion at Hospice 1. This practice was in line with the recommended hyoscine hydrobromide dose in evidence-based guidelines published for the treatment of death rattle in palliative care (Bennett et al, 2002) shown in Table 7.14.6. Deviations from this prescribing pattern in Hospice 1 occurred; when the prescribing preference of one specialist registrar was for hyoscine butylbromide, where an active decision that the sedative side effects of hyoscine hydrobromide should be avoided or where treatment had failed and an alternative agent was required.

Hyoscine butylbromide was generally prescribed for death rattle at Hospice 2. In the patients entered into the present study, the bolus subcutaneous doses of hyoscine butylbromide most commonly prescribed (for 20 patients) were in the range '40-80mg'. A dose of 40mg was administered in 98% of those cases. This indicates that the intentions of prescribing a dose range were not realised, a dose of 40mg hyoscine butylbromide being administered with only 2% doses administered deviating from this, despite nursing staff having the ability to do so. Twycross and co-authors (2002) recommended a dose of 20mg hyoscine butylbromide for bolus subcutaneous injection with a range of either 20-40mg and a dose range of 60-120mg over 24 hours for subcutaneous infusion (Table 7.14.6). At Hospice 2, the most commonly prescribed dose range of hyoscine

butylbromide for subcutaneous infusion (for 19 patients) was '80-120mg over 24 hours'. Of the doses of hyoscine butylbromide administered in this prescribed range, 55% of the doses were of 80mg. The lack of evidence or scientific grounding for dosing guidelines of hyoscine butylbromide in the treatment of death rattle is reflected in a comment in the published evidence-based guidelines (Bennett et al, 2002) 'that if a single dose of hyoscine butylbromide produces effects lasting for 1 hour, then a subcutaneous infusion of 400mg over 24 hours would be expected to be required'. This predicted dose of 400mg is not used in current clinical practice or recommended in any guidelines, notwithstanding that the use of anticholinergic agents for the treatment of death rattle in the present study are outside licensed indications and a dose 400mg hyoscine butylbromide in 24 hours would exceed the maximum stated dose in the British National Formulary (B.N.F, 2005) four-fold.

Bolus injections of glycopyrronium were prescribed less frequently; five times in the range 200-400micrograms and four times in the range 400-800micrograms. Administration of the highest dose in each range was given in 66% and 50% administration events respectively. It could be concluded that as glycopyrronium tended to be reserved for second line treatment, that there was a greater tendency to administer doses at the higher end of the range in the hope of a greater chance of response. This may be because the onset of the antisialogogue action of glycopyrronium, if this is the significant desired pharmacological effect in the treatment of death rattle, is much slower than hyoscine (Ali-Melkkila et al, 1989).

7.16.6.2 Dose intervals between administration of anticholinergic

The duration of action of the anticholinergic drugs used in the treatment of death rattle appears uncertain. The duration of the effect on saliva secretion of a single dose of hyoscine butylbromide is reported to be less than 1 hour (Herxheimer and Haefeli, 1966) and for hyoscine hydrobromide to be 2 hours (Twycross et al, 2002). On repeated administration in moribund patients the duration of action has been reported to increase, up to 9 hours (Twycross et al, 2002; Hughes et al 1996). When reviewing the observed time intervals between bolus doses of

hyoscine hydrobromide administered in the present study (Section 7.11) there appeared to be a great variation both within and between individuals. Viewing this data in isolation, it could be hypothesised that if hyoscine was having a therapeutic effect in death rattle via an anti-secretory effect, and was being given on an 'as required' basis, that the time between injections might give an indication of the duration of action of the drug. The difference in duration of action within individual patients would however not support this hypothesis. There was no particular trend to indicate that repeated dosing of hyoscine hydrobromide lead to a longer time interval between dosing and based on existing pharmacological and pharmacokinetic data (Twycross et al , 2002) this hypothesis would not seem to be supported.

By looking at this data in conjunction with the patient case profiles (Appendix I), other factors can be identified which may have influenced the frequency of administration of hyoscine hydrobromide. Patient case profile C010 where there were the most frequent administrations of hyoscine, the patient was noted to have been coughing sputum for the week before admission and received treatment with antibiotics and nebulisers, indicating the possibility that the death rattle was unresponsive to the repeated doses of hyoscine given in an attempt to reduce his symptoms. Patient case profile C012 also showed evidence of underlying chest infection. Patient C006 was receiving oxygen therapy but prior to entry to the present study had been receiving pilocarpine drops, used in palliative care as a treatment for dry mouth considered to be a side effect of opioid treatment. This questions the rationale of the seeking an antisialogogue effect of hyoscine in this patient and of an anticholinergic being the sole cause of any response in treatment of death rattle. Patient C004 was recorded to have underlying bronchopneumonia and the death rattle symptoms were reported and documented on the data collection sheet, to respond to changes in position. This patient also received diamorphine injections at the same time as the last two injections of hyoscine hydrobromide were administered, making it difficult to reach any conclusions about which drug was the effective therapeutic agent.

In addition, external factors influencing frequency of administration of hyoscine, may have been relevant to the interpretation of the results, such as the presence

of relatives, or unrelated activities or preferences of the nursing staff who would make the decision on whether to administer the drug. These observations emphasise the complexity of death rattle as a symptom and its treatment, demonstrating the difficulty in using single outcome measures in order to identify the effectiveness of treatment.

An issue which will be discussed further in the general discussion is the practice of prescribing dose ranges of anticholinergics. The dose of drug administered to the patient was recorded on the drug administration chart. No further documentation was available giving an explanation of how the nurse had decided the appropriate dose to administer. In addition without the monitoring tool utilised in the present study, there was no uniform method of recording the outcome of treatment interventions.

Very rarely were the responses to anticholinergic treatment documented in the patient's medical records, and even though the study was in place which should have facilitated and encouraged the monitoring and documentation of response to treatment, this was often not documented as fastidiously as was hoped

7.16.6.3 Guidelines for the treatment of death rattle with anticholinergic drugs

The general prescribing within the two hospices in the present study conformed to current guidelines on the treatment of death rattle which were available both to those providing specialist palliative care and to non-specialist healthcare professionals. Advice on anticholinergic dosage within these guidelines was however not always consistent. The following examples shown in Table 7.14.6.3 were readily available to the non specialist apart from those published by Bennett et al (2002) which were published in a palliative medicine journal and was the only publication to make reference to an evidence base.

Table 7.16.6.3 Dosage details from current published guidelines for administration of anticholinergic agents to treat death rattle

Summary of Guidelines	Source
HBBr 20mg sc bolus HBBr 40-40mg sc bolus , 60-120mg for sc infusion	(Twycross et al, 2002)
HHBr (400-600mcg sc bolus; HHBr 0.6-2.4mg/24hours sc infusion) HBBr (20mg sc bolus; 60-120mg/24hours sc infusion) GLY 0.4mg sc bolus;0.6-1.2mg/24 hours sc infusion)	(McMorran et al, 2005) General practice notebook www.gpnotebook.co.uk
HHBr 400-600mcg sc bolus, 0.6-2.4mg/24 hours sc infusion HBBr 20-60mg/24hours sc infusion GLY 0.6-1.2mg/24 hours sc infusion	B.N.F 49. 2005 (British National Formulary, 2005)
Some evidence for single dosing: HHBr 400mcg sc bolus, review response after 30 minutes, if effective consider continuous sc infusion 1.2-2.0mg over 24 hours. GLY 200mcg sc bolus, review response after 1 hour. Doses of 400mcg likely to produce faster results at 30minutes. Consider 1.2-2.0mg sc infusion over 24 hours depending on prognosis. (assume a single dose would last for 5 to 8 hours) HBBr 20mg sc bolus; review after 30 minutes. (Assuming a single dose of HBBr 20mgs lasts 1 hour, sc infusion of over 400mg would need to be given over 24 hours. This is substantially higher than doses used in current clinical practice.	(Bennett et al, 2002.)

Key

HHBr = hyoscine hydrobromide sc = subcutaneous

HBBr = hyoscine butylbromide

GLY = glycopyrronium

Both published guidelines as shown above and pharmacodynamic evidence (Section 2.4.6) for glycopyrronium, indicate that a response time from administration to drying of secretions was likely to be at least one hour. Unfortunately the amount of data collected in the present study was too small to draw any significant conclusions. The response time and the extent of response to anticholinergic drugs administered by subcutaneous infusion was found to be much harder to measure because of the confounding factors already discussed (section 7.11) and the unknown effect of administering bolus doses of anticholinergic against an existing background of continuous infusion.

7.16.6.4 Observations of the noise monitoring using the noise meter and subjective scoring system.

Although there was shown to be some correlation between subjective noise scoring by nursing staff and the objective noise level monitoring (Section 7.10.3) inconsistencies in the two modes of measurement of death rattle noise, observed within the patient case profiles, require noting. The nursing staff found it difficult to monitor the noise levels at the times required by the protocol. Particular issues noted to result in sub-optimal monitoring frequency were low staffing levels, and when there were other demands on their time, such as when a high proportion of the population of patients on the ward were of higher dependency. Other studies reviewed gave very few published details on exactly how the monitoring of response to interventions for death rattle were carried out. It would have been more reliable to have one observer recording all observations, however this was not practical as some patients were monitored for several days. Patients were entered into the study at different times of day and night. Staffing levels being generally much lower at night than during the daytime, may have compromised the quality of data recording. This raises the question of the reliability of data in previous studies.

Previously published reports into the effectiveness of anticholinergics contain no comment on additional and concurrent interventions, which in the present study were often observed to occur at the same time as administration of anticholinergics.

Nursing staff also noted that external factors such as relatives talking, affected the readings on the noise meter. It was also noted that nursing staff seemed reluctant overall to use the noise meter, particularly where relatives were present and frequently cited 'relative's anxiety' as a reason not to use the noise meter. The general discussion will explore further whether the noise level itself is the key factor in triggering the decision to treat death rattle, or whether this is a more complex multifactorial issue, involving the quality of the death rattle noise, the ward workload status, and accompanying anxiety and pressure from relatives

(Chapter 10) An exploration of the carer attitudes and the focus group discussions will reveal more on these underlying issues (Chapter 9).

7.16.6.5 The influence of nursing patients in single or double rooms on the treatment of death rattle

The data collected for this part of the present study were too small to show any trends. There were too many variables which could confound the results such as the number of single rooms available at any one time, which would in turn be influenced by the cohort of patients currently being cared for in the hospice.

Because the entry criteria for the present study were such that the patient received anticholinergic treatment for death rattle, the data collected did not support the identification of any patients who developed death rattle but may not have anticholinergics administered because they were in a single room. In addition, the hospices practiced a policy of nursing patients in the most appropriate environment wherever possible. It is possible that some patients were moved to a single room because they developed noisy breathing.

Results from the focus groups (Section 9.3.7.3) implied that often patients and relatives would be given the option of a single room (if available) if the patient developed death rattle. Nursing in a single room could therefore reflect an outcome, arising from the development of death rattle, rather than indicating a reduced tendency to treat patients for death rattle if they were in a single room.

7.16.6.6 Evidence that factors in the patients previous medical history may influence the control of symptoms of death rattle.

7.16.6.6.1 Evidence of current or recent chest infection prior to entry of study

The small numbers recruited in the present study prevent any firm conclusions being drawn with regard to the relationship between the presence of a respiratory infection or other pathology such as heart failure and difficulty in controlling death rattle. However all of the patients in this study who had death rattle symptoms that were difficult to control had underlying indicators recorded in their medical records, or evidence from the drugs prescribed on drug administration charts, that could be identified at the time of study entry, which may have predicted that the death rattle would be resistant to treatment with anticholinergic agents (Section 7.12). Although the data collection chart prompted nursing staff to record whether the patient had been noted to have green or yellow sputum on study entry, as an indicator of possible respiratory infection, this was not found to be a reliable indicator in the present study. Ellershaw and co-workers (1995) had anticipated that the presence of respiratory tract infection would be associated with persistent respiratory tract secretions but their study found a low association between infection and presence of respiratory tract secretions (7%). This was commented to be in contrast to Schell (1972) who reported that over 60% patients who died with cancer had evidence of respiratory tract infection at post mortem.

Morita and co-workers first investigated the relationship between death rattle and pulmonary infection or pulmonary oedema (Morita et al, 2000) using the criteria that either new crackles had been detected on physical examination or new infiltrations on chest x-ray film observed within the previous week. The authors acknowledged that this assessment of pulmonary oedema had not been validated. Pulmonary infection or oedema was detected in 81% patients with death rattle 12 hours after initial assessment, in 85% of patients 24 hours after initial assessment and in 97% of patients within a few hours of death. In a later study (Morita et al, 2004) a 68% incidence of pneumonia was recorded in patients

with 'bronchial secretions'. The fact that this study identified few patients with green or yellow sputum at entry to study could again be linked to the poor diagnostic value of this observation.

Although the presence of respiratory infection in these patients is therefore likely, diagnostic practices such as sputum culture or chest X-ray assessment which may be routine in hospital would not routinely be carried out in the hospice setting. Although antibiotic treatment for control of death rattle which has a likely infective origin would seem a rational intervention, there is often reluctance to prescribe antibiotics for patients with a diagnosed infective cause to their symptoms as the physician has a role to neither 'hasten or postpone death' but has an obligation to provide symptom control.

Treatment of death rattle with antibiotics therefore poses a difficult ethical decision for the practitioner and the patient, as there is the possibility that doing so might artificially prolong life. Currently, the administration of an anticholinergic, does not have an associated effect of possibly prolonging life. This raises the question of whether it is ethical to prescribe and administer anticholinergics to a patient in order to treat death rattle which is likely to be infective in origin, when the benefits of such treatment are likely to be minimal and with the possibility of subjecting the patient to adverse effects. The development of a protocol or procedure to highlight infection as a cause of death rattle which is unlikely to be responsive to anticholinergic treatment might encourage alternative measures such as thorough explanation to relatives or the consideration of symptomatic antibiotic treatment.

7.16.6.6.2 Evidence of other possible risk factors for the development of death rattle.

A diagnosis of primary lung cancer, pneumonia and dysphagia have been identified as factors which were significantly associated with development of bronchial secretions (Morita et al, 2004). Hydration status of the patient, oedema or pleural effusion did not appear to be related to development of bronchial secretions. No clinically significant difference was reported between dehydrated

and non-dehydrated patients in the development of respiratory tract secretions (Ellershaw et al, 1995). All non-dehydrated patients however developed respiratory secretions by the time of death compared with 89% of dehydrated patients (as defined by serum biochemistry). Non-dehydrated patients also showed a trend towards persistent secretions which were less amenable to treatment. In the present study three patients had subcutaneous fluids continued: Patient SM101 was reported to have died peacefully, patient SM114 had a subjective noise score of 1 at death and patient SM102 had a fluctuating noise score, but was reported to be quiet and peaceful at the time of death.

Administration of subcutaneous fluid tends to be routinely practised in some hospices and not others, however from the literature it would seem that this factor alone it is unlikely to increase the risk of developing death rattle or be a significant factor in treatment. The numbers in the present study are too small to confirm these findings but follow this trend.

At least two patients were consented into the study who had received radiotherapy to their salivary glands. One of these did not require any anticholinergic treatment as they did not develop noisy breathing. Patient SM119 was entered into the study and received three bolus injections of hyoscine butylbromide. Lack of monitoring data prevent any conclusions being drawn as to whether treatment was effective, although the repeated administration may indicate that this did not control secretions. However the medical records contain documentation that the patient may have aspirated fluid. This questions the rationale of firstly prescribing anticholinergics for noisy breathing that could be due to aspiration (which also is known to have occurred to a Hospice 1 patient in the present study, who was consented but not monitored) and also the rationale for the use of anticholinergics in a patient where the salivary glands have been irradiated.

7.16.6.7 Explanation of the process of death rattle to the patient or relative

All patients in the present study received the patient information leaflet on death rattle (Appendix B). As referred to in Section 7.14.3 on difficulties experienced

with the consenting procedure for the present study, explanation regarding this symptom however needs to be delivered in a timely and sensitive manner both, to patient and relatives. Patient's are usually unconscious or unaware of this symptom by the time it occurs (and therefore asking for informed written consent for entry to the study may have unnecessarily caused anxiety to the patients involved in this study – although there is no evidence to support such a hypothesis.) Many of the previous studies have commented on the value of explanation to the relatives although do not postulate how this might best be done. An information leaflet may be of value. Further work is required in this field.

7.16.6.8 Limitations of the study outcome measures used to assess effectiveness of treatment for noisy breathing.

The standard grading system described by Back and co-workers (2001) was employed in this study and used on the data collection sheet. This system has since been used in other studies allowing some comparisons to be drawn (Morita et al, 2004). The intention was that objectivity could be introduced to noise level assessment by using the noise meter.

The statistical correlation and observed inconsistencies between the treatment outcome results using the noise meter and the subjective noise scoring, has been discussed. (Section 7.14.6.4) . Confounding factors associated with a greater risk of developing death rattle which is more resistant to treatment, have been identified in previous studies (Morita et al, 2004; Kass and Ellershaw, 2003) and in the present study. Palliative care treatment is always tailored to the individual, resulting in varying concomitant medication regimens which may also have an effect on outcome.

The results of the noise monitoring section of the present study demonstrated the difficulties encountered when asking nursing staff to record data in the palliative care environment where the method of measurement was seen as an unnecessary intrusion for the patient and their family. Poor levels of documentation of response to treatment were noted, even whilst the study was being carried out when motivation should have been high to complete data

recording forms. This questions the reliability of documentation recorded during routine circumstances, and the subsequent evaluation of this data in retrospective studies.

These observations of the limitations of the present study highlight areas of questionable reliability and validity in the methodology of previous studies particularly when these studies are used as evidence on which to base treatment guidelines.

The term 'noisy breathing requiring medication' could not reliably be used as an indicator that death rattle was present - or of the loudness of the rattle. From the observations in the present study – interventions such as turning were not recorded fastidiously, making it difficult to determine whether a drug intervention, or turning or re-positioning had produced a change in the rattle. (This was experienced at first hand in one patient where the patient's position was changed whilst the nurse went to draw up the medication for administration. On returning to administer the injection the rattle had resolved. On the data collection chart however, the repositioning was not recorded and the resulting improvement in death rattle would have been attributed to the drug administration).

The fluctuating nature of the death rattle noise recorded in this study, also questions the validity of sampling the death rattle noise intensity at regimented time intervals, as this may not give an accurate picture of the overall course of the 'burden' of death rattle noise.

Further discussion will be presented in the light of results from the patient carer questionnaires and focus group elements of the study (Chapters 9 and 10).

7.16.6.9 Conclusions from the subjective and objective noise scoring of treatment of death rattle with anticholinergics

Although the number of patients recruited into this study was too small to support statistical testing of the results, there were more positive outcomes in terms of

reduction of death rattle noise in patients treated with hyoscine hydrobromide, and this was mainly with bolus injections of 400 micrograms. Patients treated with subcutaneous infusions of hyoscine butylbromide in conjunction with bolus doses of hyoscine butylbromide did not achieve such positive responses overall in terms of reduction of death rattle noise. What is not clear is whether the anticholinergic drug itself was having an effect or the methods of administration. As only one patient received an infusion of hyoscine hydrobromide, the infusion of hyoscine hydrobromide and hyoscine butylbromide could not be compared. A previous study observed that patients receiving infusions of hyoscine hydrobromide were just as likely to receive bolus injections of anticholinergic within six hours of death as those without infusions (Bennett et al, 1996) which supports the findings in the present study. The findings of the present study do not support suggestions that early treatment with anticholinergics, given by subcutaneous infusion, result in greater reduction in death rattle.

8 Results of the relative and carer interviews on death rattle treatment

8.1 Introduction

In order to explore the belief commonly held by healthcare professionals that patients receive treatment for death rattle symptoms mainly for the benefit of attendant relatives or carers, brief structured interviews were conducted as explained in Section 4.9. For the purposes of the interview, the term 'noisy breathing' was used instead of death rattle.

8.2 Results of interviews with relatives and carers

Only a small number of interviews were conducted overall, four from each hospice, representing 29 % of patients entered into the study in Hospice 1 and 19% of patients entered into the study in Hospice 2. The results from each hospice were analysed together and the responses for each of the questions addressed in the structured interview are shown in Table 8.2.1 and Table 8.2.2. All interviews were carried out in a quiet room, outside of the ward environment. Hand written notes were taken by CH (or the nurse in one case) during or immediately after the interview.

Table 8.2.1 Results from relative or carer structured interview relating to their experiences of distress caused by death rattle during the study.

Structured interview questions	Patient SM121	Patient SM118	Patient SM102	Patient SM112	Patient C005	Patient C018	Patient C014	Patient C013
Have you felt distressed by the patients noisy breathing?	A little	A lot (Relative was a health-care professional with experience in the field.)	A lot	No	A lot	A lot	A little	A lot
Could you express the effect of the noisy breathing on your overall feeling of distress or emotion?	"More distressing for another relative."	Small to some effect. More distressing for other relatives	Very large effect		Very large effect	Large effect	Some effect. "When rattle stops think they've stopped breathing"	Large effect
Do you feel that treatment to try and reduce noisy breathing has helped you?	Yes	Yes	No. Now it is not working		Yes	No		Difficult to know
Any other comments?	None	Relative worked in an elderly care unit where patients were often given suction. Considered drugs were a better option.	Although drugs were felt to help at first, the effect had reduced and the relative was asking for something stronger.		Noisy breathing was much better 45 to 60 minutes after drug treatment. The relative was able to go back and sit in the room.	Relative did not feel that the syringe driver had helped. Suctioning had helped and the relative would have liked this performed for the patient more often though nurses were reluctant.	If rattling could be cured, it would help the patient. Patient had rattly breathing at home before coming into hospice. The relative listened to it as a sign that the patient still breathing.	Constant gurgling was a problem but seemed to respond to hyoscine.

Table 8.2.2 Results from the relative or carer structured interview relating to their perceptions of the distress caused to the patient by death rattle during the study

Structured interview questions	Patient SM121	Patient SM118	Patient SM102	Patient SM112	Patient C005	Patient C018	Patient C014	Patient C013
Do you feel that the patient is, or has been distressed by noisy breathing?	A lot	A little " More distressed from pain"	A lot	No	A lot	A lot	A lot	No
To what extent do you feel that noisy breathing is adding to the patient's overall distress?	"No distress" Felt that drugs were working	Some distress	Much distress		Much distress	Much distress	Much distress	No distress
Do you feel that the treatment to reduce noisy breathing has helped the patient?	Yes	Yes	Yes When it was working		Yes	No Suctioning helped.	Some effect. "Breathing eased with massage". "No", although first injection seemed to calm the patient.	Yes
Subjective noise monitoring data	Yes	Yes	Yes	Yes	Yes	No.	No	Yes
Noise meter data available	Yes	No	One point	No	Yes	No	No	Yes

Five out of the eight respondents (62.5%) expressed the opinion that the 'noisy breathing' caused 'a lot' of distress to the patient. Three respondents however considered that there was little or no distress to the patient (37.5%).

When asked if they found this personally distressing, again five (62.5%) responded that 'noisy breathing' distressed them 'a lot' and three (37.5%) that it did not distress them. As seen in Table 8.2.1, these respondents were not necessarily the same respondents who expressed the opinion that the patient was distressed by the breathing.

Four respondents (50%) reported that the 'noisy breathing' contributed a large effect in their overall state of anxiety at that time, two (25%) considered the effect to be greater for other family members.

Four (50%) of respondents expressed the opinion that overall the sound of 'noisy breathing' contributed greatly to the distress of the patient. One respondent considered that 'noisy breathing' caused some distress and one believed that the drug treatment was effective. No data was available for one patient.

Four of the respondents (50%) considered that the drugs administered had helped the patient, though one expressed this in terms of '*calming the patient*' rather than specifically reducing the 'rattly breathing'. Three respondents (37.5%) considered that the treatment had helped them personally (in an indirect manner), however one added that the drug administered had reduced 'noisy breathing' at first and had a reduced effect on a later occasion.

When free comments were invited only two respondents (25%) considered that the drugs had been successful in reducing the 'noisy breathing', one expressed the view that that '*something stronger was now needed*', another indicated that suctioning had been more effective. None of the respondents made any reference to side effects.

8.3 A comparison of the responses from the relative or carer interview with the noise monitoring data available for those patients.

The responses from the carers or relatives with regard to their perception of the effectiveness of treatment and perceived levels of distress were compared with the data recorded in the patient profiles which may be found in Appendix I. Two of the patients in Hospice 1, where relatives were interviewed, did not have accompanying noise data recorded in the patient profile.

8.3.1 Comparison of the responses from the relative or carer interview with noise monitoring data for patients in Hospice 1.

A relative of patient C013 was interviewed in the middle of the period of monitoring after some subjective improvement in death rattle had resulted after drug treatment. This improvement was however later noted to occur just prior to a period of high subjective and recorded noise level. This was an example of a relative who expressed the opinion that although the patient did not seem distressed, they experienced a lot of personal distress from the patient's symptom and believed that the drug treatment had helped the patient. The subjective noise scoring by the nursing staff indicated that drug treatment had not produced a reduction in noise level, the score still remaining at 2. A similar trend was shown by noise meter monitoring although only performed for a short period of time (Appendix I).

A relative of patient C005 who was interviewed had previously declined the nurse's offer for any anticholinergic drug intervention for this symptom. However, as time had elapsed, the family who were present with the patient in a single room, found the noisy breathing more difficult to cope with. Interestingly, the nursing staff did not acknowledge any subjective improvement in the noise score although the noise meter indicated a reduction in the level of noise (by 65 %) after one hour and fifteen minutes. Further reference to this particular patient was made in the focus

group discussion with healthcare professionals (Chapter 9), this patient was remembered as one who had secretions that were very difficult to control.

8.3.2 Comparison of the responses from the relative or carer interview with noise monitoring data for patients in Hospice 2.

Both subjective and objective noise scoring data were available for patient SM121 (Appendix I). The relative of the patient perceived that the anticholinergic drug treatment had helped the noisy breathing but the subjective noise scoring by the nursing staff showed no change in death rattle in response to drug treatment. Nursing staff also noted in the patient's medical records that suction had been given with effect. This latter point was not volunteered by the relative, who in fact may not have known (it is not known whether this relative was present at the time that suction was given). Nursing staff also recorded in the patient medical records, that '*drugs were given without effect*' and readings from the noise meter, although only recorded at two time points, showed a trend towards an increase rather than a decrease in noise level. Nursing staff also documented in the medical records that this patient had a dry mouth. This was not recorded on the adverse event chart and was not mentioned by the relative. The patient had a syringe driver administering hyoscine butylbromide 80mg, diamorphine 20mg and midazolam 5mg over 24 hours for 15 days.

The Interview was carried out on 4/11/03 after the syringe driver administering the drug combination had been started, but nursing staff did not monitor noise scores until 13/11/03. The interview therefore may not have reflected any changes in the pattern of the death rattle, this may explain why the relative had considered that the drug treatment was successful.

The relative of patient SM118 was interviewed at the start of a monitoring period which lasted nine days. The corresponding data collected by nursing staff on the response of death rattle to treatment was subjective only and the noise meter was not used (Appendix I). The interview was conducted at a time, during which hyoscine butylbromide was being administered to the patient via the syringe driver.

In addition, subcutaneous bolus injections had been administered which appeared to have some effect on the death rattle for short periods of time but warranted increasing dosages. The relative was not interviewed again at a later period to avoid distress.

The interview with the relative of patient SM102 was carried out on the third day of monitoring (Appendix I). Drug treatment, which had appeared to settle the death rattle initially, seemed to be less effective, resulting in the administration of additional bolus injections together with administration of hyoscine butylbromide via a syringe driver. The patient, with a primary diagnosis of non small cell lung carcinoma, was still conscious and there was a noticeable degree of family anxiety, this was also reflected in the anxiety demonstrated during the interview.

This short interview with the relative of patient SM112 was carried out by a nurse with previous research background together with the relative. The patient profile (Appendix I) did not show drug treatment to be particularly effective in reducing 'noisy breathing', anticholinergics being administered both by a syringe driver with additional hyoscine butylbromide and glycopyrronium by bolus injection. The nursing notes documented in the patient's medical records report that drugs were given for bubbly breathing but that the patient was not distressed. Not all of the questions were addressed during the interview; the reason for this was unclear.

8.4 Discussion

The small number of relatives and carers interviewed during this study was disappointing. The reasons for this were varied. It was difficult to predict when relatives were likely to be present as the hospice rules regarding visiting times were often relaxed during the terminal phase so that relatives could visit at any time, making it difficult to conduct interviews. Although a consultant and a nurse in each centre had agreed to ask questions of the relative, the same issues of timing applied. Often the perceived level of anxiety among the relatives was given as a reason by the nursing staff, that the family should not be approached. None of the interviewees approached to take part in the study refused to do so directly.

The timing of the interviews in the present study only provided a snapshot in time, during a symptom course which continued for variable lengths of time, and often had a very fluctuating pattern. Some of the interviews took place during a period of relatively quiet breathing and may have missed a subsequent increase in the noise level or the persistence of the death rattle. It was not considered appropriate to do sequential interviews in these cases, as although bereavement staff were aware that the study was being conducted and that some relatives may later have issues to discuss, it was considered that multiple interviews could cause a disproportional focus on the death rattle.

The interview in the present study did not include a question asking whether reassurance or explanation about the death rattle symptoms had been offered by the nursing staff, and if so, whether this offer had been taken up. Information on this subject was not volunteered by any of the interviewees in the free comment section

The timing of the interview had been carefully chosen to be conducted during the period of treatment for noisy breathing, so as not to rely on the relatives recall of events surrounding an emotional period and to avoid the immediate period of grief after the patients death. A previous study had aimed to evaluate relative distress when death rattle was present by questioning relatives when they returned to collect death certificates. Eight responses were obtained out of a total 25 relatives Back (2000). Distress of relatives was reported to be a main reason for not pursuing response from relatives. In the present study, the period immediately post bereavement, was not considered to be an appropriate time to question relatives about death rattle.

An alternative method of collecting information from relatives about their experiences of death rattle, at a time later in their bereavement was considered in the present study. The possibility of inviting bereaved relatives to attend a focus group, was considered when it became apparent that recruitment of relatives as planned was leading to poor recruitment (Section 4.4.2). In view of the time that would be involved to gain ethical approval, this was not subsequently thought to be feasible at this stage of the present study.

After the data collection period for this study had finished, a thesis was published entitled 'Death Rattle: An exploration' (Wee, 2003) which unknown to the author of the present study at the time, had sought to establish related facts about death rattle. Wee (2003) invited patients who had been bereaved, for interview to discuss issues including death rattle at the time of their relatives death between two and four months after bereavement. The precise methodology was adjusted between two phases of the study, as some relatives accepted the invitation to interview where their relatives had not had death rattle symptoms. Themes explored focussed on how much distress was caused to the relatives by the patient's death rattle. Other issues including the effect of intervention and whether any explanation had been given by the healthcare professionals was also explored.

8.5 Conclusion

The resulting numbers of participants for this part of the present study were too small to draw any firm conclusions although there was a trend for a greater number of relatives to report that the noisy breathing of the patient had caused them personal distress. Two respondents admitted that they found the death rattle sound more distressing for themselves than they considered it to be distressing for the patient. It was not clear to what extent any informal input had been made for these families by nursing staff to offer an explanation of the death rattle and whether this helped them.

Respondents opinions were split on whether interventions had helped the patient both in terms of symptoms and distress, although suctioning was felt to be effective by one relative where this had been performed. Only three of the respondents expressed the opinion that, at the time of the interview, they considered that the drug treatment was currently helping the noisy breathing for themselves or the patient. The perception of the effectiveness of treatment assigned by nursing staff and relatives did not correlate.

The method of recruitment of relatives for interview used in the present study, was not felt to be as helpful as hoped with regard to whether the relatives felt that the

intervention had helped to alleviate any distress. One advantage of conducting the interview in a prospective manner, in relation to the treatment of death rattle symptoms was that responses would not be dependant on recall of events after bereavement. The time course of the death rattle symptom was variable however and the interview could only afford a snap-shot of the relatives experience up to the time of the interview. It should be recognised that the degree of distress of relatives is likely to be multifactorial, particularly at such an emotional time, and distress due to death rattle would only be considered to be one factor in relation to that distress. Further discussion on the distress caused to relatives will follow in Section 9.3.7.6 along with results from the focus groups with health care professionals.

9 Results of the evaluation of palliative healthcare professionals' perspectives on the treatment of death rattle from focus groups.

9.1 Introduction

Focus groups were conducted as described in Section 4.10 over a period of 12 months. The transcription of each focus group session recording was carried out by the author as soon as possible after conducting the group. Five focus groups were conducted: one group with in-patient nursing staff from Hospice 1 and Hospice 2, one group with home-care nursing staff from each hospice and one with specialist registrars training in palliative care in hospices around the West Midlands NHS Region. The dates that focus groups were conducted along with the number of participants in each group are shown in Table 9.1. The groups consisted of between 6 and 7 participants except the Home Care Group at Hospice 1 which only included four participants.

Table 9.1 Details of the Focus Groups conducted to explore healthcare professionals' views of the treatment of death rattle.

Study Centre	Date	Focus Group	No. Participants	Status of participants
Hospice 1	22.5.02	Home Care Team	4	Home care clinical nurse specialists
Hospices bases across the West Midlands Region	11.6.02	Specialist registrars	7	Specialist registrars (6) at different stages of specialist training plus one visiting registrar from elderly care.
Hospice 1	19.6.02	Ward nursing staff	6	Ward sister, staff grade nurses (2), auxiliary nurses (2), aromatherapy nurse practitioner (1)
Hospice 2	8.4.03	Ward nursing staff	7	Staff grade nurses (4), auxiliary nurses (3)
Hospice 2	12.6.03	Home Care Team	6	Home care clinical nurse specialists

Although all planning according to the methodology (Section 4.10.2) was carried out prior to each focus group, the first two groups conducted at Hospice 1 demonstrated that this did not guarantee that focus group participants would arrive at the pre-arranged venue on time, or be available at all. Managers had agreed to the groups being carried out within the working day. The first focus group was planned using prior written personalised invitations, together with a reminder. However only the author was present at the appropriate time as staff were unable to leave the ward area owing the high dependency of patients on the ward at that time combined with staff absence because of sickness.

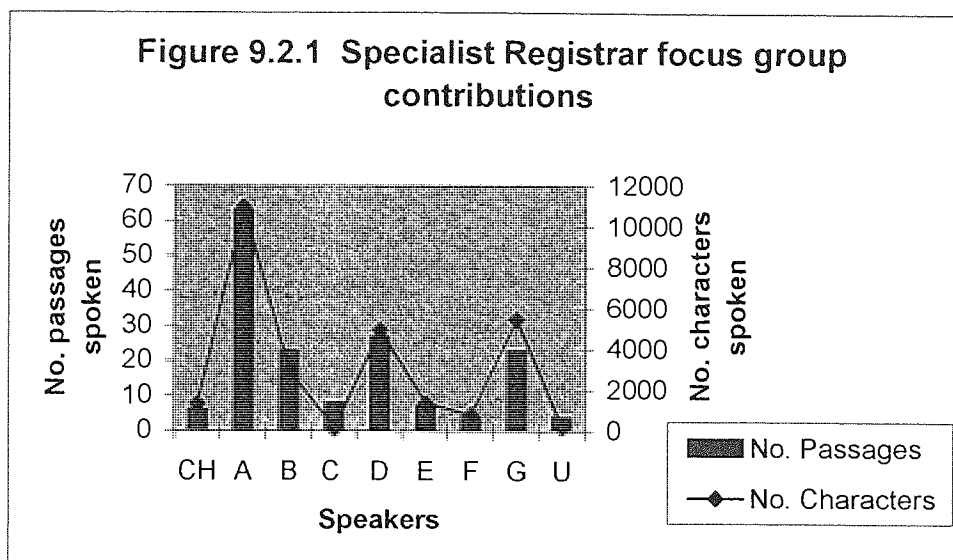
A second date was then arranged with the ward sister. A different approach was taken by inviting staff who were present in the hospice on that day. This was more successful in terms of focus group attendees. The process of introducing the format of the sessions, the context in which the focus group would be conducted and obtaining consent from the participants was however more time consuming. Subsequent sessions were planned with this in mind. The focus groups with the specialist registrars and the Home care team at Hospice 2 took place within protected learning time.

All of the focus group sessions lasted between 45 minutes and one hour, partially dictated by the time that staff were available, however all the focus groups achieved their objectives during that time period.

9.2 Observations of the dynamics of the focus groups

9.2.1 Specialist Palliative Care Registrars Focus Group

The specialist palliative care registrar group had the greatest number of participants and took place within pre-arranged protected learning time study day. All of the palliative care specialist registrars were present, plus a registrar from elderly care speciality. A representation of the participation (in terms of passages and number of characters spoken) by each of the speakers can be seen in Figure 9.2.1.



The number of passages corresponds to the number of times the participant spoke a continuous phrase and the 'characters' give an approximate comparative volume of speech.

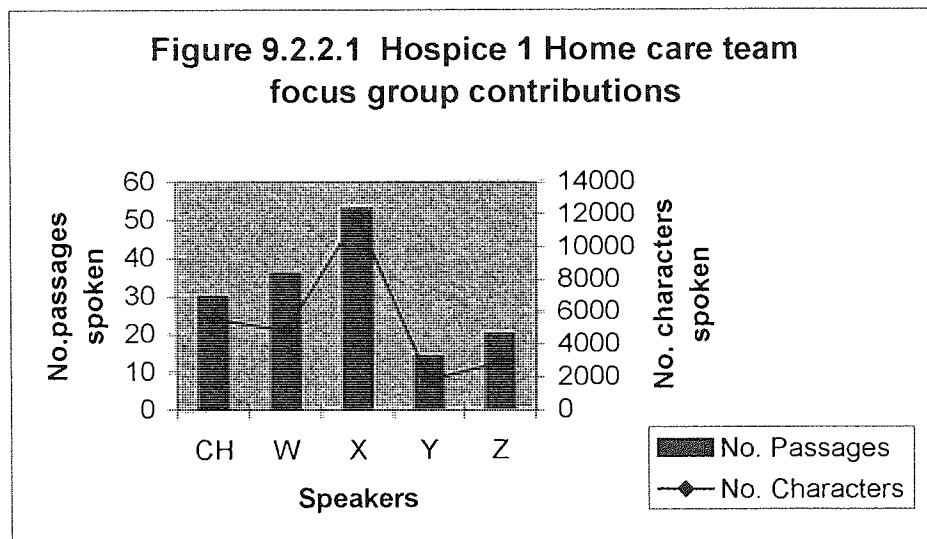
Overall, the participation of the specialist registrars group flowed well requiring the least input of all the groups from the facilitator (CH). One participant had significant prior background knowledge of the published literature relating to anticholinergic treatment of death rattle, having produced treatment guidelines of the study subject at another hospice. The next three participants showing highest level of participation in discussion were close to completing their specialist registrar training, suggesting that experience, confidence in knowledge of the subject, or perceived hierarchy within the existing group may have been a contributing factor. Each contributor appeared prepared to make statements and ask questions of one another and there were no instances when opinions seemed to be swayed or changed in response to any one participant's comments.

At the end of the focus group session, the group as a whole expressed their satisfaction at having the opportunity to discuss the subject of the treatment of death rattle in such a forum.

9.2.2 Hospice Home Care Team Nursing Focus Groups

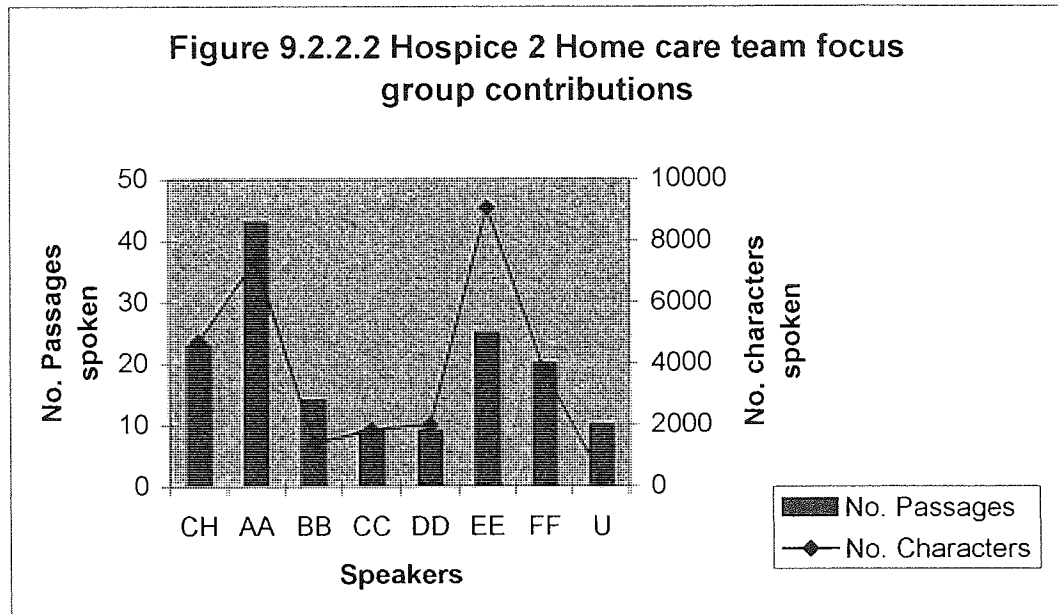
The nursing staff working in the Hospice Home care teams are palliative care clinical nurse specialist who have undergone specialist training in palliative care and have considerable prior experience of nursing, from different nursing backgrounds in both hospital and community.

The input from the facilitator (CH) in the Home care team nursing groups was higher than that for the specialist registrars, but similar for each hospice group. The Hospice 1 focus group included only four participants. Although arranged at a time to be convenient to the team, on the day not all the invited participants were available to take part owing to work commitments. The difference in contributions to discussion in this group did not correlate to a greater number of years of palliative care experience within the Hospice Home care team and is shown in Figure 9.2.2.1.



The focus group with Hospice 2 Home care team took place in protected learning time and followed an audit presentation on prescribing trends for syringe drivers, including the use of anticholinergics, by the Home care team leader. It was not considered that this variation would greatly affect the group responses in the focus group discussion which followed directly after the presentation. The data presented was a descriptive illustrative account of the prescribing habits from the Hospice 2 Home care team and the focus group discussion was started immediately after the presentation of data on anticholinergic use, providing an appropriate and relevant introduction to the focus group discussion.

Contributions to discussion were highest from the audit presenter in terms of number of times input occurred (Figure 9.2.2.2). This may have been due to familiarity with the subject, experience or perceived hierarchy within the group dynamics. The reduced number of characters however suggest that speech passages were shorter, in contrast speaker EE interjected less often but with longer passages of speech. Again years of experience within the team setting did not appear to be directly related to the volume of contribution.

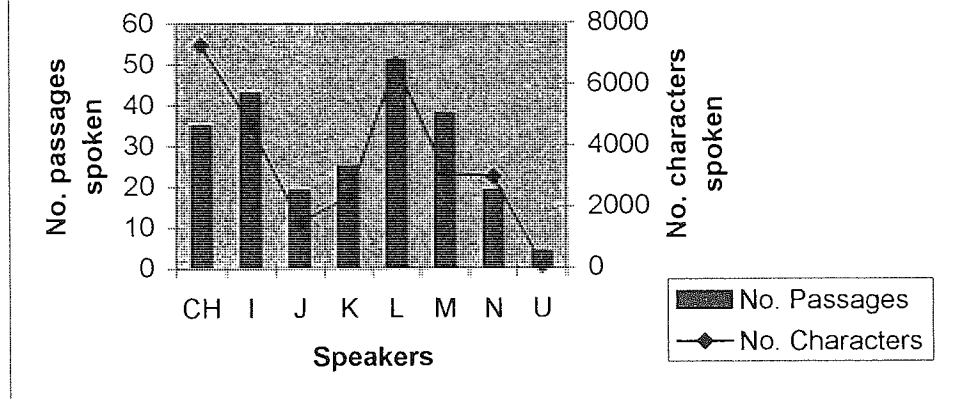


These two groups gave insight into particular issues faced by patients being cared for in the community.

9.2.3 Ward nursing staff focus groups

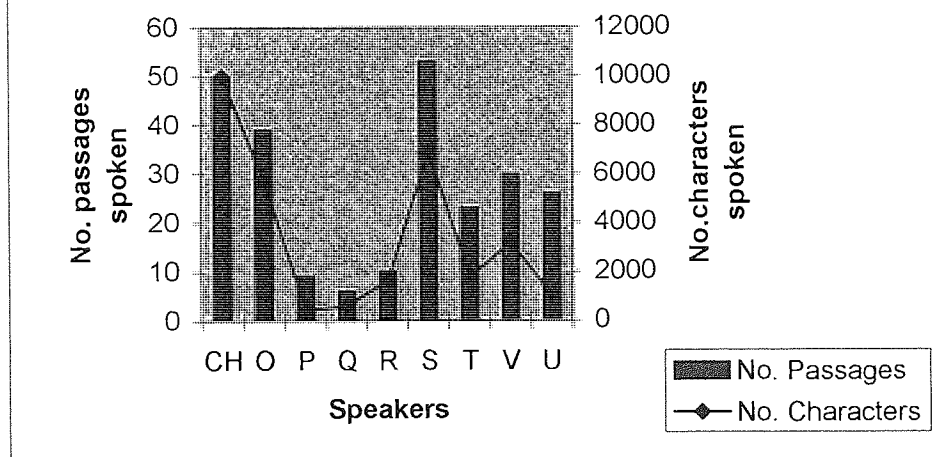
Both of the ward nursing staff focus groups required relatively more input from the facilitator (CH); Hospice 2 more than Hospice 1. All of the ward nursing staff participating in the Hospice 1 focus group had been working at the hospice for some considerable time. Most contributions were made by two senior qualified staff, but also by an experienced auxiliary nurse (Figure 9.2.3.1).

Figure 9.2.3.1 Hospice 1 ward nursing staff focus group contributions



No speakers were influenced to change opinions following others' speech. Of all the groups, the ward group in Hospice 2 flowed least well, requiring more input from the facilitator (CH). This may have been due to two relatively new members of the nursing staff and ward nursing team. The highest contribution to discussion was made by an experienced qualified nurse (Figure 9.2.3.2). However the small contributions from the two less experienced nurses, which occurred later on during the discussion, contained very valuable comments.

Figure 9.2.3.2 Hospice 2 ward nursing staff focus group contributions



Coincidentally neither of the two tapes for the session in Hospice 2 were very clear resulting in the highest proportion of unidentified speech (U) for this group. The room used in Hospice 2 was in the middle of the hospice building and air conditioning may have been the cause of interference causing muffling of voices on one of the tapes.

9.2.4 Consent issues

During the preparation and conduction of the focus group process, no participants expressed any difficulties with the consenting process or fed back any issues arising out of the conduction of the focus groups.

9.3 Analysis of focus group transcripts

Analysis of the content of the focus group transcripts was carried out as described in Section 4.10.3. Coding for the themes emerging from the focus groups. The coding spine developed in shown in Appendix H.

9.3.1 Knowledge, opinions and beliefs about anticholinergic drugs used to treat death rattle.

9.3.1.1 Introduction

In each focus group, nursing staff talked initially about the anticholinergic drug with which they were most familiar. This was generally the first choice of anticholinergic agent used within their own hospice (hyoscine hydrobromide at Hospice 1 or hyoscine butylbromide at Hospice 2). Hyoscine butylbromide was often referred to by the brand name Buscopan during the focus group discussion. This was also true of the registrars, however their rotation around the hospices and general medical experience resulted in a broader discussion.

9.3.2 Hyoscine butylbromide

9.3.2.1 Knowledge, opinions and beliefs about hyoscine butylbromide in the treatment of death rattle.

Doses of hyoscine butylbromide administered, advised or prescribed by medical and nursing staff, were acknowledged to vary by all groups where this drug was used. The specialist registrar focus group discussed doses, and whether there were differences between giving one off (bolus or 'stat' doses), and administration by subcutaneous infusion in a syringe driver. The problem of the inconsistency of dosing advice or prescribed doses were also discussed at length in the Hospice 2 Home care team group, and the Hospice 2 ward nurse group. This was well illustrated by the comment from the Hospice 2 Home care team, where the tape recording of the session began at discussion of the audit results:

Hospice 2 Home care AA. *'What's the dose range of people having Buscopan for secretions? As you can see some started at 40[mg], some at 60[mg], some at 80[mg] and some at 120[mg]. Now I wasn't quite sure of the logic of all that really. My practice for what it's worth is to start at 120[mg] and I've often heard [physician] say there's no point going in at less than that for secretions.'*

There followed discussion and controversy about their own different practices and recommendations.

9.3.2.2 Timing of administration of the hyoscine butylbromide.

In addition to the dose, the timing of initiation of treatment was considered to be important by both focus groups at Hospice 2. There was a generally held belief that the earlier that hyoscine butylbromide was initiated, the more effective it was in relieving death rattle.

Hospice 2 Home care EE. *'I find that 80[mg] works as long as you set it up as soon as they start to go chesty. If they've been chesty for over 24 hours, you're on a bit of a losing battle. You know you can increase, you start at 80 [mg], within no time you've got to 120[mg]. And you can even go, like there's one at 160[mg]. But I find it all depends on the starting dose of the drug as to the effectiveness of it, for myself.'*

Hospice 2 ward nursing staff group also commented on the importance of early administration of hyoscine butylbromide in relation to the start of 'rattly breathing'.

Hospice 2 ward staff S. *'I think if you catch the rattling quickly, when it's fairly quiet.'*

Specialist Registrar E. *'Over the couple of years that I've been in palliative medicine, I've got a sort of feeling that the general view is that if you don't treat at the beginning then you're not going to get control of it. Is that true?'*

9.3.2.3 Effectiveness of hyoscine butylbromide for treating death rattle.

Hospice 2 ward nursing staff focus group expressed the view that hyoscine butylbromide was generally effective at treating death rattle, (although 'effectiveness' was not defined) but qualified that this was not so in all cases and that effectiveness might vary with duration of therapy. However the Hospice 2 Home care team, felt that effectiveness might be related to the starting dose.

Hospice 2 ward staff V. *'It [hyoscine butylbromide] seems to be alright in the early stages but as time goes on and the secretions get more or it's more static..... Then it doesn't work as well really.'*

Hospice 2 ward staff T. *'Effective' [hyoscine butylbromide]*

Hospice 2 ward staff S. *'Effective , for certain cases' [hyoscine butylbromide]*

Hospice 2 ward staff V . *'Sometimes they're effective, sometimes they're not though are they?' [hyoscine butylbromide]*

Participants in the Hospice 1 Home care team had different opinions on the effectiveness of hyoscine butylbromide.

Hospice 1 Home Care X. *'Personally I don't use Buscopan for secretions'*

Hospice 1 Home Care W. *'I don't either. That's because I was always told it didn't work for secretions'*

It was acknowledged in several groups, that centres that used hyoscine butylbromide as a first line agent, did so because of cost considerations, based on reports in the literature. Although the reference was not quoted it was assumed that the reference was to Bausewain and Twycross(1995).

9.3.3 Hyoscine hydrobromide

9.3.3.1 Knowledge, opinions and beliefs about hyoscine hydrobromide for the treatment of death rattle, including transdermal formulations.

Staff who had worked in the palliative care team at Hospice 1 were more familiar with the use of hyoscine hydrobromide to treat death rattle and most of the comments on this drug came from these groups, together with comment from some of the specialist registrars.

Doses of hyoscine hydrobromide prescribed or administered were more standard, however there was still some discussion around whether effectiveness was dose related. Hyoscine hydrobromide was usually administered as a bolus injection on an inpatient unit. Prescribing hyoscine hydrobromide in a syringe driver was less common for inpatients, but was practised in the community more commonly. Two participants in the home care team did not consider that hyoscine hydrobromide was very effective in a syringe driver, and this was discussed in comparison to the use of the transdermal formulation of hyoscine.

Hospice 1 Home care X. *'No I don't like the patches and I don't like the driver. I'd rather give stat doses [hyoscine hydrobromide]. I think they work better.'*

However alternative views were also held:

Hospice 1 Home Care W. *' I haven't found that it's [hyoscine hydrobromide] been very beneficial in the syringe driver. I don't know whether it's because the dosage isn't high enough or whatever, but if you give a stat dose and then a few hours later*

check back and they've still been quite bubbly whereas with the patches, I don't know why, but they seem to be more effective.'

Hyoscine patches and their perceived effectiveness in different situations and side effects were discussed in all the groups. Their value, in all groups, was considered to be greater in the community setting rather than the in-patient setting. In the ward nursing staff focus group in Hospice 1 related a belief that 'power' of the injection over 'the patch' might be greater for some patient's relatives. Generally the transdermal route was thought to be of greater value to patients with problems of oral secretions, who were not in the terminal phase of illness, such as Motor Neurone Disease, rather than for death rattle in the terminal phase.

Although it was generally acknowledged by all the groups that the transdermal hyoscine patches were associated with a high risk of causing confusion and agitation in the elderly. It was also acknowledged that the transdermal route could be so effective, that the resultant dry mouth and sticky secretions could be worse and therefore that they were not ideal for all patients. Adhesion of the patches was noted to be an occasional problem.

Hospice 1 ward staff S. *'When they've worked [hyoscine patches] they've made a difference to mouth secretions. But if somebody has got really confused with them and you've taken it off, it's quite dramatic to see how they've improved. They're usually the elderly.'*

Hospice 1 ward staff O. *'Or if they're very sweaty and they tend to slide off all the time from where they're positioned'.*

The value of relatives being able to apply the hyoscine transdermal patches to the patient themselves was also felt to be beneficial for the relative or carer, providing that the correct instructions were given on how to apply them and that they were encouraged to ring for help if the patient became confused. Confusion tended to be associated particularly with the use of transdermal hyoscine patches.

9.3.3.2 Effectiveness of hyoscine hydrobromide to treat death rattle

The following comments regarding the effectiveness of treatment of death rattle were made by the ward nursing staff focus group from Hospice 1. Although hyoscine hydrobromide was not mentioned directly, this was the standard treatment for death rattle at this site.

Hospice 1 ward staff I. *'Do you get the impression we're not convinced at all and it's something that we've all done. And done for years. And tried to do everything else. All the other sort of measures. The moving, the explaining and the reassuring, The spending time with. And the relatives ask 'Is there something that you can give? Will you ask the doctor?' and 'Oh I'll ask the doctor' and you get the feeling the doctor's probably thinking the same. 'Oh, well, we'll give some hyoscine.'*

Hospice 1 ward staff L. *'But I don't know that it really works to be honest. It doesn't seem to make it any quieter. Do you think so?'*

Hospice 1 ward staff I. *'I think if you ask people they would. A high proportion of people would say it doesn't work. You give it because it's prescribed. We're expected to give it. We're expected to give it a try, but most people will say 'well it doesn't work':'*

Hospice 1 ward staff I. *'I'd just like to know if anybody anywhere is really convinced it helps ? Ever?'*

Hospice 1 ward staff K. *'But saying that, very often, as it doesn't make a difference. It's still there.'*

In the specialist registrar group, one participant expressed opinion on efficacy.

Specialist registrar G. *' But I don't actually think I works. I don't think it dries up death rattle.'*

Specialist registrar A. *'We didn't know... [referring to a local audit]*

Specialist registrar G. *'I think it dries up the mouth'*

This exchange occurred during discussion of an audit which had been undertaken by one of the registrars in the group at their hospice, as part of a guidelines development process introduced because of a perceived lack of effectiveness of current treatment regimens. The new guidelines proposed earlier prescribing of hyoscine butylbromide and glycopyrronium within that unit. The complexity of outcome assessment of treatment was further explored by the registrar group whilst recounting an individual case:

Specialist registrar C. *'it comes back down to nurses confidence really, with the drug. They've always used hyoscine [hydrobromide] and therefore they're confident in that. And the lady that we used Buscopan on, when she had a stat dose of 20 [mg] and it worked, because I was there and I saw it work. But then she had a driver with just 60 [mg] [Buscopan] in it and apparently it didn't work. And she had one dose of hyoscine hydrobromide and it did work..... Was it just because we didn't put enough Buscopan in the driver?*'

All groups expressed varying opinions about the mode of administration, dosage and efficacy of the anticholinergic drugs. All focus groups were aware that hyoscine hydrobromide could potentially cause more side effects. They also considered that hyoscine hydrobromide might be more potent, tended to be given as bolus doses and was more expensive than hyoscine butylbromide.

9.3.4 Glycopyrronium. :Knowledge, opinions and beliefs about glycopyrronium in the treatment of death rattle.

Glycopyrronium was not used as a first line agent for treating death rattle at either hospice. Participants in the four nursing groups expressed a general lack of knowledge about the drug and its use. In the specialist registrar's group, the participant who had audited anticholinergic guidelines, demonstrated in depth pharmacological knowledge of the drug when questioned by other group members. In other focus groups such questions were mainly directed towards CH. Glycopyrronium was considered by all groups to be prescribed and administered when all other measures or 'first-line' anticholinergic drugs had failed to control the death rattle. Opinions on the effectiveness of glycopyrronium were not expressed.

The value and rationale of administering glycopyrronium at this time, as a 'last attempt', was however questioned:

Hospice 2 ward staff O. *'Sometimes it's too late isn't it?'*

Hospice 2 ward staff S. *'Yes'*

Hospice 2 ward staff T. *'By the time you've got to that stage sometime, you've got no time. They've died.'*

Hospice 2 ward staff S. *'But it does seem to have some effect doesn't it? When the Buscopan doesn't. Don't know why but.'*

Hospice 1 Home care AA *'I've used it occasionally, usually when Buscopan has failed. And I think on the odd, odd occasion, it seems to have helped'*.

9.3.5 Discussion of the side effects of the anticholinergics drugs.

All nursing staff in the focus group at Hospice 1 were aware of the potential for patients becoming confused following administration of hyoscine hydrobromide. They reported that relatives would sometimes notice dry mouths. They also expressed thoughts that hyoscine hydrobromide was often the last drug that was given before death. Nurses in both ward groups expressed the possibility that administration of hyoscine might hasten death, although it was appreciated that hyoscine was generally given as (or because) the patient was dying imminently. Ward staff described the difficulty in differentiating between agitation in a patient, and other side effects which might be drug related or due to the dying process.

Hospice 2 ward staff S. *'I think because they're so ill anyway, the patients, when they come into that stage, it's hard to know whether the dry mouth is Buscopan or just the illness.'*

9.3.6 Factors which might affect palliative care healthcare professionals' decision on whether to use anticholinergics to treat death rattle.

9.3.6.1 Knowledge of the pharmacology of anticholinergic drugs and decisions to administer or prescribe.

The limited knowledge of the basic pharmacology of the anticholinergic drugs among the focus group participants has already been discussed, together with their belief that the earlier the drugs were started in terms of death rattle symptoms, the greater the likelihood of having an effect on death rattle. The groups also indicated that the choice of anticholinergic drug administered may affect the outcome although there was no consensus of opinion between the groups on a preferred anticholinergic drug. Side effects (constipation, dry mouth) were recognised as a theoretical problem but not often commented on as a significant problem at the end of life. It seemed therefore that the decision on which drug to administer or prescribe within the hospice was based on familiarity.

Hospice 1 Ward staff group L. *'The thing is, we all know it about isn't it? Even outside of palliative care. Hyoscine. I said I didn't know what that was [glycopyrronium] .I'd never heard of that. But obviously I've heard of hyoscine. So we tend to go to with that because we know it and it's been used a lot'.*

Hospice 1 ward staff I. *'It's the one that's prescribed'*

Hospice 1 ward staff L. *'That's the one you think about.'*

Hospice ward staff N . *'Is that the one that's been around the longest?'*

Hospice 1 Home Care X. *'I think the other thing is that hyoscine hydrobromide is the drug of choice here, which is where we work. So to a certain extent you fall into line with the system they use on the ward or the preferences. But four years later on I have my own thoughts about what works and what doesn't. I'd be quite keen to use this [glycopyrronium].'*

Hospice 1 Home Care X. *'But I think the other thing with glycopyrronium is that we're not so familiar with interactions, that's my concern with putting it in the driver'*

Lack of knowledge regarding compatibility of glycopyrronium with other drugs in a syringe driver was a reason cited that could have influenced the decision against its use. Cost was also often cited as being perceived to have an influence on the choice of anticholinergic drug used within hospice environments.

Nurses knowledge of the available anticholinergic agents seemed to be drawn from past working experience, or interaction with colleagues from other palliative care units. During focus group discussion, questions were directed towards CH, asking if studies had shown that glycopyrronium was successful in treating death rattle.

Although the specialist registrars were more aware of the pharmacology of anticholinergic drugs than the nursing groups appeared to be, from the questions asked and answered, it appeared that only one registrar participant with a particular interest in the subject showed evidence of pharmacological or evidence based argument during the discussion.

Hospice 1 ward nursing staff discussed briefly the fact that they were familiar only with hyoscine hydrobromide. Hospice 1 ward nursing staff were not allowed to prescribe but could exercise discretion of choice if two anticholinergics were prescribed on the 'as required' section of a patient's drug administration chart. Ward nursing staff at Hospice 2 were in a similar situation with regard to choice of drug, although they were often able to exercise their discretion in the choice of a dose for administration within a specified prescribed range. Home care nurses were in an environment where they would be advising General Practitioners, sometimes in choice of drug and dose, but not having direct prescribing responsibility themselves at the time of the present study.

Both Home care focus groups and specialist registrar focus groups (apart from one participant) expressed compliance with the existing prescribing practices of their unit, rather than expressing knowledge of evidence based prescribing.

9.3.6.2 Knowledge of the underlying pathology of death rattle and decisions to prescribe or administer anticholinergic drugs

Two focus groups (Home care Hospice 2 and Specialist Registrars) discussed the relevance of assessment of the underlying pathology in patient's developing death rattle. The terminology 'type 1' or 'type 2' death rattle was only raised once in the specialist registrar focus group. In the specialist registrar group at least one member was aware that the literature suggested a link between certain pathologies and likelihood of developing respiratory secretions in the dying phase. However participants expressed the opinion that this may not have affected their decision to advise or prescribe anticholinergic treatment.

In most groups the terms or descriptions of 'respiratory distress' or 'breathing difficulty' including 'breathlessness' were recognised and acknowledged as being different from 'secretions' causing death rattle or noisy breathing during the terminal dying phase, in the course of the focus group. No definitions were given at any point however and when the term 'secretions' was used it was sometimes difficult to decide on precisely how these terms had been chosen within certain sections of conversation, and whether this was confined to the terminal phase.

The following quotes illustrate these issues:

Hospice 2 Home Care 2 EE *'I can't honestly say that there was any benefit because they were so full of fluid on their lungs and I think that the two patients I used it on had pulmonary oedema.'*

In relation to a recent case where a patient with advanced disease had developed noisy secretions,

Specialist registrar G ..*'and hyoscine was given and it was pulmonary oedema that the patient had'*.

9.3.7 The place of non-drug treatment of death rattle

9.3.7.1 Positioning of the patient

Discussion in the focus group of Hospice 1 ward nursing staff indicated that in the ward environment, it was not routine nursing practice to administer anticholinergic drugs as first line treatment for death rattle, even if they had been prescribed. Rather, changing the patient's position in the bed would be the first line of intervention, at the same time, acknowledging that sometimes routine changing of the patient's position can sometimes worsen death rattle. Carrying out general nursing care for the patient such as routine mouth care and spending time with relatives was also identified as having a vital role in general care of the patient with death rattle.

Home care team focus groups also acknowledged the value of patient positioning as an effective intervention for death rattle but qualified this by saying that in some situations, relatives in the home environment were resistant to changing the position of the patient and often wanted the patient 'left alone'. One member of the group also commented that death, in the home environment, often occurred soon after repositioning.

Hospice 2 Home care EE. *'well families will say 'I don't want him touched, I don't want him moved' and the nurses go in and you go back the next day and he's still in the same place....'*

Hospice 2 Home care BB. *'And if someone is in the last hours of their life and you start to move them, then sometimes they die while you're moving them and their families would get upset, so you'd rather give them that last bit of time..'*

Hospice 2 Home care AA. *'You have to use your judgment don't you, with everyone. One of my patients would lie over the side of the bed leaning on a stool and no matter what position you put her into, that's where she got herself back to. And you know you just have to accept that that's where they're comfortable...'*

9.3.7.2 Information on death rattle for carers and relatives

All of the focus groups discussed the issue of giving information both to carers and sometimes patients, about death rattle and interventions that could be made for treatment. Generally all groups considered that information on the basic underlying cause of death rattle was important for the relative if the patient had developed that symptom.

Hospice 1 ward staff L. *'I think maybe, well obviously relatives don't understand the dying process do they? Where as we're aware that all these things are just part of dying.'*

Hospice 1 ward nursing staff discussed how and when information would be offered to patients and carers, and that it could be inappropriate to ask patients about the treatment that they might wish to have for death rattle, for example in an advanced directive. One view was that indiscriminate delivery of information on death rattle could increase anxiety.

Hospice 1 ward staff N. *'Do we make everybody aware of the potential of it and actually increase the anxiety. Thinking is this going to happen or not?'*

The following contribution was from a nurse who had recently joined the hospice:

Hospice 2 ward staff R. *'Maybe if the relatives, you know, were told that this could be a possibility as something that's happening, you know, and given to expect that, maybe they wouldn't have such a problem with it'*

Hospice 2 ward staff V. *'if patients have got this noisy breathing then the first thing I would do is to talk to the relatives and say that I don't think this is causing them any concern. But if you're getting distressed then maybe we could put some music on, or change the position of the patient,'*

The discussions within the focus groups indicated that preparation and explanation about death rattle to carers and relatives, prior to symptoms occurring was beneficial. This was more likely to be carried out more by the home care teams and less often by the ward staff.

Hospice 2 Home Care EE *'It's the reassurance I've found with patients, that once I've gone through what's happening. Why they've got noisy breathing, the drugs we're using which are trying to help the situation, but they never put an expectation to it. You'll find the edge of their concerns come out because they're starting to understand why they've got noisy breathing'*

Hospice 2 Home care EE. *'I've been a ward sister myself and I can honestly say myself that when they're in the hospice I wouldn't have gone through that point. Until it started to happen. And as they started to get chesty I would say, "You know this is something that starts to happen when they start to get...."*

Hospice 2 Home Care FF. *'Because unless, in the inpatient unit they specifically came and asked what might happen. I don't think, you know, you never went into as much depth because there were people around.'*

The situation on the ward was considered to be subtly different from the home care situation as the main caring role was usually taken over by the nursing staff in the hospice, whereas at home the relatives would have more control. The frequency with which relatives visited patients in the hospice also varied from those patients who constantly had relatives in attendance at this stage and those who had visits less frequently. In some cases, relatives would be called in if it was considered that the patient was near the end of life.

Hospice Home Care 2 FF *'Where as of course in the home, the family are usually there with the patient all the time'*

Another view from the Home care team focus group (Hospice 2) was the comparatively short time available during a visit to the family in a community setting in which to impart a relatively large amount of information. Nurses believed that patients were actively given more verbal preparation for symptoms which might occur, including death rattle, in the community setting and that this would happen less in the ward environment where there was an assumption made that nurses were available for consultation, if the relatives needed information.

The registrars' focus group mentioned information to the relatives briefly, as part of a step-wise plan of interventions to treat death rattle.

9.3.7.3 Distraction therapy for relatives of patients with death rattle.

'Distraction therapy' for patient's relatives, such as music was highlighted as an alternative intervention tool, in conjunction with an explanation about death rattle symptoms in one ward nursing staff focus group.

The use of single rooms for patients with death rattle was discussed in both ward nursing staff groups. Although it was agreed that moving a patient into a single room could alleviate some anxiety for nursing staff and relatives who thought that death rattle signified a loss of dignity for the patient, or could be distressing to other patients. The enclosed environment of the single room could have the effect of focussing the relative's attention on the noise of death rattle. It was suggested that some relatives did want to focus on the breathing noise and would sometimes refuse the offer to have music or television as a distraction.

Hospice 1 ward staff K. *' Because we do usually get the chance to put a person into a single room don't we? If the chance is there. So they're not often left in a four or two-bedder, with other patients. But even we're aware that it can be frightening for other relatives that are there with the patients.'*

Hospice 2 ward staff T. *'But there aren't the distractions in the single room for the relatives, are there? Like there's distractions, they can actually have an excuse to sort of, listen to other things. But in the single room they're just there. And that's all they hear! And they focus. And you try to introduce things like music but other than that.'*

Hospice 2 ward staff S *'That's in a single room, that's quite distressing. They just want to I think to focus in to the patient. They wont have anything, they just all sit there, looking at this.'*

9.3.7.4 Suctioning as an intervention to relieve death rattle

The subject of suction was dealt with differently by the groups and much of the time involved their perceptions of how other people felt. The practicalities of accessing suction in the community would be difficult unless the patient had a suction machine available at home, which would only usually be the case for patients with a tracheostomy or neurological disorder. Participants in the Hospice 1 Home care team focus group had never used suction as an intervention for death rattle for patients in the community. However they did report that families who had seen suction used on other patients, perhaps in hospital, had occasionally requested it for their relative.

The views on the appropriateness and efficacy of suction to treat death rattle was variable. Ward staff in Hospice 1 considered that it had a place in the context of patients who had overwhelming secretions (before the dying phase) rather than those with death rattle.

Hospice 1 ward staff L. *'But it seems really cruel to suction doesn't it? When they're At that stage of their life'*

There was some discussion over whether suction was of benefit to the patient. However, it was recognised that some patients required suctioning and that it would be performed if clinically necessary.

Hospice 1 ward staff I. *'We did have to do suction in the end there because she was literally swimming'*

Hospice 2 ward staff.S. *'It's a bit invasive and in our experience it doesn't seem to help does it?'*

One specialist registrar commented on suction, expressing the opinion that the nurses were reluctant to suction patients:

Specialist registrar F. *'I think the nurses are quite reluctant to suction patients as well. They'd rather give an injection, where as sometimes by the stage the secretions are troublesome, it will need suctioning actually to remove those.'*

9.3.7.5 Issues regarding death rattle treatment for patients in the community environment

Practical issues affected the choice of drug used to treat death rattle in the community. These included drug availability, and the availability of district nursing staff to administer drugs. For example, administration of a bolus injection could be more problematic in the community, making hyoscine patches, which the carers could apply, or the administration of the anticholinergic by infusion in a syringe driver requiring only one daily visit, a more practical solution. Availability of palliative care drugs in the community was unpredictable in some areas at the time of the present study, particularly outside normal working hours. Dose and choice of drug administered was often dictated primarily by drug availability.

The contrasting care environment between ward and community was highlighted by both Home care focus groups. Most relatives or carers in the community did not have close expert supervision;

Hospice 2 Home care. BB. *'It was also different on the ward because there were nurses their to care for the patient. Whereas in their own home, the relatives have got to cope.'*

The level of explanation given by nurses to families in the community was considered to be greater, because the contact time with specialist nurses was relatively short. The time spent on the preparation of families for a death in the community was not thought, by the Home care teams, to be so proactive in the hospice in-patient environment. The first part of the following quote from Hospice 2 Home Care EE was given in Section 9.3.7.2. The respondent went on to say:

Hospice 2 Home Care EE. *' But I notice when I'm in the home, I'm looking for key moments, like [colleague] said and when they say to me "So what will happen towards the end?" They're my key things to start preparing them.'*

Hospice 2 Home Care. FF. *'In the inpatient unit, unless they specifically came and asked what might happen. I don't think, you know, you never went into as much*

depth because there were people around. And also as an in-patient the family wouldn't be there all the time.'

In the community other health carers delivering care directly to the patient, (for example district nurses) were usually in close communication with the Home care team members. One Home care team member related the experience of having to justify treatment decisions to the patient's community healthcare team, particularly if the decision had been taken not to treat death rattle. Although this was only mentioned by one member, it was considered to be another factor which could affect the decision to treat in the community which may not occur in the hospice environment for nursing teams.

Hospice 2 Home care team DD. *'.. and if you had a patient that was bubbly and you weren't treating them, you also have the opinions of all the other healthcare professionals involved, the district nurses ringing up and saying "What on earth are you doing? You know this patient's very bubbly!" So you have to give rationale to them as well, why you're not maybe doing things that they think you maybe should.'*

9.3.7.6 Focus group discussion around whether the patient or the relative is more distressed by death rattle.

All focus groups embraced discussion around the distress caused by death rattle. In the first ward nursing staff focus group (Hospice 1) the subject was introduced very early in the session.

Hospice 1 ward staff M. *'Prescribing decisions.[pause] Is it for the patient or relative, that they prescribe these drugs?'*

Hospice 1 ward staff K. *'Um I think a lot of the time it's for relatives. And it doesn't actually do the patient any good at all.'*

Hospice 1 ward staff M. *'I don't think it does any harm'*

Hospice 1 ward staff K *'No but it doesn't actually make things that much better. '*

Discussion in this focus group then continued on the subject of whether treatment was given for death rattle more frequently if it was thought that other people (visitors or patients) were aware of the noise. Hospice 2 ward nursing staff group also expressed their concern for causing distress to those around the patient.

Hospice 2 ward staff V. *'It's just distressing'*

Hospice 2 ward staff P. *'An awful lot to hear their loved one making this terrible noise'*

This group then also expressed their own feelings of distress in this situation:

Hospice 2 ward staff O. *'You feel helpless I think, a lot of the time'*

Hospice 2 ward staff S. *'The rest of the ward as well. I think that's really distressing for the other patients.'*

Hospice 2 ward staff O. *'For everybody yeah'*

Hospice 2 ward staff S. *'It's distressing for you as well as staff isn't it? You feel as if you're failing'*

Specialist registrar F. *'I think the majority of the time it is the relatives that we treat. Because by the stage that patients have death rattle, they're not aware of it, in the majority of cases, and if they are aware enough to say 'I've got rattly secretions' then there are other ways perhaps of trying to help treat that. So I think it is often the relatives.'*

Specialist registrar D. *'I don't think it's completely unreasonable to be treating the relative though'*

The Home care teams expressed the opinion that families were often very distressed by death rattle. They believed that giving prior information and reassurance was very helpful for families caring for the patient in the home environment. Distress to the patient from their own death rattle was only considered to be an issue if the patient was alert. Members in the groups however recalled patients who they believed had been distressed by bubbly breathing, or that when

they had been questioned closely by the family to categorically reassure them that the patient was 'not distressed', were unable to defend their position.

Hospice 1 Home care X. *'..But I would still have to question or still have to say, well I can't put my hand up in the air and categorically say that the patient isn't distressed by it....'*

Ward nursing staff in the focus group in Hospice 1 were unclear about their position regarding the ethics of administering drugs to the patient in order to 'treat the family', as they perceived their role to help the families as well.

Hospice 1 ward staff M *'None of this is given for the patient, it's all given purely for the relatives.'*

Hospice 1 wards staff K. *'Yes I think so'*

Hospice 1 ward staff N. *'I think also maybe, that the thing for the patients would be dignity. I sort of think that if they were nice and, the thought that they were nice and quiet'*

Hospice 1 ward staff N. *'There was almost a loss of dignity surrounding the noise, it wasn't natural, and it was almost like an embarrassment'*

The aim of relieving a relative's distress lay in belief by the nursing staff that death rattle resulted in a death that was not peaceful for the relatives and that could subsequently become an important long term issue in bereavement.

Hospice 2 Ward staff O *'I think it's something that relatives remember. As not being a peaceful death'.*

The complexity of making this assessment on behalf of a third party was expressed both in a response to a question about outcome measures in studies looking at treatment for death rattle, and to a question raised by relative a about whether a patient was distressed.

Specialist registrar A. *'Well I think degrees of relative distress are almost impossible to assess'.*

Specialist registrar D. *'There's a lady that I saw yesterday, well it was her husband that was dying and he had been started on Buscopan. It had worked, and interestingly I went in yesterday morning and I thought he probably needed the dose increasing, partly because of the discussion we'd had about the previous patient but partly because I thought that the secretions were still a problem. But She [patient's wife] didn't, and I think actually if I had increased it up, I probably would have increased it for the wrong reasons and he was perfectly settled and not distressed at all. So I think that even with the relatives, the amount that they can tolerate varies.'*

Only one participant in one focus group embraced the issue of administering an 'intervention' (suggestions for such interventions were offered in the discussion) directly to relatives.

Hospice 1 ward staff I *'It would be nice if we could give something to the relatives actually'*

9.3.7.7 Opinions and beliefs about benefits versus risks of giving anticholinergic drug intervention to treat death rattle.

All of the groups held a general perception that hyoscine butylbromide did not cross the blood brain barrier and therefore produced less side effects than hyoscine hydrobromide.

Questions were posed regarding side effects versus benefits, but no answers were offered from within the focus groups.

Specialist registrar B *'Is it actually more comfortable to be a little bit noisy and moist than to have a dry mouth?'*

There were however issues raised by the ward nursing staff in both groups, surrounding the complex issues of giving drug treatment for symptom control around the time of death, both for the nurses and the relatives:

Hospice 1 ward staff L. *'Well I've not been here for a long time, but certainly when they've given it [hyoscine hydrobromide], well here it doesn't seem to be very long*

before the patient has died.... It's like you hear the nurses saying "But if I give that, they won't have much longer". They're nervous to give it.'

Although this statement was rationalised by the following comment,

Hospice 1 ward staff M. *'Because they are literally dying when it's given'*

Hospice 1 Home Care Z. *'I think the biggest thing about using the injections as stat doses in the last few hours of life. However many times you say that the injection isn't going to make any difference, this is purely for the secretions, I've had to listen to them say to me so many times. "Oh the nurse gave him the injection and he died a little bit later" and the inference is that it was the injection.'*

9.3.7.8 Focus group members' opinions about prescribing or administering anticholinergic drugs to treat death rattle

There was a general feeling of uncertainty as to whether anticholinergic drugs were effective for the treatment of death rattle, but an acceptance that such therapy was routine practice. Some statements were made which indicated that because of the lack of evidence base, and uncertainty in their own minds of whether the death rattle would respond to anticholinergics, that other factors had a greater bearing on whether or not anticholinergics were prescribed or administered. Only one participant in one focus group was unsure about the benefits or ethics of administration of anticholinergics for death rattle and expressed a feeling of being pressurised by other healthcare members to make the intervention, against their own beliefs. When questioned by another group member about whether they considered that administration of anticholinergics caused the patient harm, or was just not beneficial, the respondent expressed that they thought that it decreased the patient's quality of life.

One member of the ward nursing staff focus groups expressed feeling obliged to administer anticholinergics, because they had been prescribed as a treatment option.

Hospice 1 ward staff I *' We give it [hyoscine hydrobromide] because it's prescribed, we're expected to give it.*

Some members of the specialist registrar's focus group who did not routinely prescribe 'as required' anticholinergics, expressed having experienced pressure from nursing staff to prescribe anticholinergics, particularly out of hours. Members of the specialist registrar focus group reported that they would often succumb to pressure to prescribe the anticholinergic being requested by the nursing staff rather than prescribe the drug of their choice. It was commented that this decision may be influenced by the nurses' confidence in the effectiveness of a particular anticholinergic.

Specialist registrar D. *'That's what I wonder. How much of it is that we're doing something and how much of it is.....'*

Specialist registrar G. *'I hate using them and I find that when I'm on call. I get called by somebody at five to midnight.. "Can we give some hyoscine". I feel that I'm being bullied you know because I'm, you know I'm quite vulnerable at midnight.. and it's very hard when you're not with the patient, to say, to argue the case that I don't actually believe in this drug and I don't think, I don't like prescribing it for anybody.....'*

Specialist registrar D. *'Do you feel that it does harm, or just does no good?'*

Specialist registrar G. *'I feel that it probably does harm, from a quality of life point of view. I think that patients are lying there with advanced disease, unable to express their distress and they get drugs to make them drowsy and then. When they're even less able to explain their distress, and then get sort of agitation, various other side effects, dry mouth, feel like they're choking, that kind of thing..... and I think that the drug causes those symptoms.'*

A doctor who had worked closely with the Home care team, expressed that they had not often been asked about treating death rattle and assumed that this was an area where the Home care nurses felt confident in their treatment recommendations.

9.3.7.9 The need to act to relieve perceived distress in others.

The characteristic of the need to intervene in any way, in order to relieve the distress of others was expressed in all focus groups:

Specialist registrar group D. *'But there are situations when we do treat noisy breathing, almost for the sake of doing something for our benefit or for the nurses' benefit and for the relatives' benefit. And it's almost like your colleague was making a contrast between a situation where she actually, definitely wanted to do something that she knew was going to be effective, rather than do something that we probably all do a bit, for other reasons.'*

Hospice 1 ward staff N. *'Yes 'cause it eases my conscience.'*

Hospice 1 ward staff O. *' and as nurses, do we not always feel, that we have to physically do something? Um, it's good for us as much as it's sort of good for everybody isn't it? To be seen to be doing something. It looks as if we're trying to be positive. Whether it works or it doesn't work doesn't seem to come into the equation sometimes I think.'*

Hospice 1 ward staff I. *'You can obviously do a lot else but sometimes they want to see you give something medical and scientific and, that the doctors prescribed and the doctors advised to have. That's palliation isn't it?'*

Hospice 1 ward staff I. *'Palliation of everyone involved, including ourselves sometimes'*

The following comments expressed the power of medical intervention:

Hospice 1 ward staff I. *'I think the problem is it is such an awful thing for people to sit and listen to. It has got such awful connotations for other people visiting other people. Um and its just that feeling that you've got to try and do something about it. You can explain and use other measures but I still think....'*

Hospice 1 ward staff I. *' ..and the injection is seen as a very positive and a scientific and you know, comfort to them'*

Hospice 1 ward staff I. *'And if you put it in a syringe driver, that wouldn't work. It would work from the patient's point of view, but then you'd be saying to the relatives. Well there is medication in the syringe driver, then they'd be saying "Well it doesn't work".'*

Nursing staff expressed the view, particularly in the in-patient units, that nursing staff were there to *'keep hope going'* and that there was an expectation that the deaths occurring in hospices should be good experiences.

Hospice 2 ward staff S. *'It's deluxe dying here isn't it? You know what I mean? Because it's a hospice'*

Hospice 2 ward staff V. *'They expect a good death'*

9.3.7.10 Overall perceptions of anticholinergic drugs for the treatment for death rattle

The following quotes summarise the overall opinions of the focus groups on the way in which anticholinergic drugs are currently used to treat death rattle.

Hospice 2 home care AA. *' I just find that you can be more confident perhaps saying that, you know, "If I give this for the pain it should settle" or "If I give the for the restlessness she'll settle". But I'm not so confident to say that if I give this for bubbly breathing, it will disappear or improve.'*

Specialist registrar D. *'Which also comes back down to well, does it actually work? Or is it just what everybody thinks works that matters?'*

Specialist registrar C. *'But it's such a hard thing to assess whether it works, that's why it's so much a cultural decision rather than a scientific decision. Because we don't know really, whether it helps the patient...'*

9.4 Discussion

9.4.1 Methodology

Although initially there were some problems with ensuring participant attendance at focus groups at the arranged time, it was possible, with persistence, to adapt and open the invitation process that allowed the staff who were available, to participate. This did not compromise the composition of the group. Only the first Home care focus group had a reduced group size. Morgan (1998) recommended that group sizes should have between 5 and 7 participants, on the basis that increasing the group size, increased the number of less active participants a finding shared by Smith (1999). There was evidence that the participating staff found participation in the groups a positive experience. The ideal situation for conduction of the focus group with the hospice staff was during existing routine protected learning time.

The groups consisted of individuals who were familiar with the subject of death rattle, and who, apart from the registrar group worked together as a team. The registrar group were however an established group, used to being together for education purposes. The participation of the group members may have been influenced by team dynamics, but no one member seemed to obviously feel inhibited from contributing to the discussion at any time. Discussion flowed with less input from the facilitator in those groups with most experience of using anticholinergics.

The groups were facilitated by the author without an assistant moderator, owing to time, funding and resource constraints. This did not compromise the running of the groups, or the accuracy of recording of activities, as the subject of discussion was familiar to all participants and the author. In retrospect, it would have been useful to explore the ethics of the decision to treat patients for the symptom of death rattle, and as facilitator these issues may not have been fully explored, in an attempt not to direct the discussion in a particular direction.

Limitations of the focus group methodology in the present study included the smaller than intended number of focus groups which were held, owing to time factors and lack of support from one other invited palliative care centre. Because of

these issues it can not be said that the conclusions reached are based truly on grounded theory (Glaser and Strauss, 1967), as although emerging theories were followed as each focus group was conducted, it is not certain whether these were followed through to saturation, although no new themes had emerged from the last two focus groups.

In reporting the speech it was felt that in view of the different work environments of each group that it was important to appreciate this factor within the report.

9.4.2 Focus group analysis

Coding was carried out using an axial coding (Krueger, 1998) using the NVivo software to assist in coding and retrieval of text. Content analysis was used only to provide a description of the group's background which was considered to be important in the interpretation of the context of the data. The data itself was analysed using a thematic approach (Joffe and Yardley, 2004) coding not just words, but also relying on interpretation of the data for latent meaning. A system of inductive analysis and coding was also followed (Bloor et al, 2001) where thematic coding was driven from themes emerging from the data, rather than using a previously constructed coding scheme based on prior researched knowledge. Joffe and Yardley (2004) however commented, that the researcher's knowledge and preconceptions, inevitably influence the identification of themes.

9.4.3 Summary of views expressed during the focus groups

9.4.3.1 Treatment and explanation of the symptom of death rattle.

The global knowledge base of the focus groups regarding the pharmacology of the anticholinergic drugs when used in the treatment of death rattle was based on experience rather than evidence. As this experience had often been confined to one particular drug, no comparisons could be drawn between different anticholinergic agents. There was confusion over the most effective dosage

regimen of the anticholinergic drugs but a belief that treatment initiated earlier in the development of death rattle would be more successful.

Side effects of the anticholinergic agents were recognised and generally thought to be undesirable, but it was acknowledged that differentiation between side effects and other symptoms in a dying patient was difficult.

In contrast with evidence in the literature (Morita et al, 2004; Kass and Ellershaw, 2003) no focus groups identified any particular diagnosis to be linked to a greater risk of developing death rattle. The difficulties of differential diagnosis between death rattle and other underlying pathology such as pulmonary oedema was acknowledged, particularly by the registrar group, however this was not clear in the nursing groups.

Although it was agreed by the nursing groups that changing the position of the patient would be the first line of treatment, the success of this or other non-drug treatments was uncertain. Nursing staff believed that an explanation of death rattle to the relatives was very important, particularly in the care of patients dying in the community environment. However proactive offering of information was less frequent in the ward environment where explanation was offered on a more passive basis.

9.4.3.2 Distress from death rattle.

Generally group members thought that the patient was not distressed by the symptom of death rattle and that treatment given was aimed at relieving the distress of the relative. The underlying reason for this was a belief that death rattle would lead to problems in bereavement. At the time of the present study there was no published evidence to support or refute this belief, however since then, publication of findings from interviews with bereaved patients have confirmed that although many relatives expressed negative feelings about hearing the sound of death rattle, there were a much wider and complex spectrum of influences on relatives. Continuing distress and sadness in bereavement was described owing to loss of a loved one rather than the sound of death rattle itself (Wee, 2003). Focus group members also voiced a perception of 'peer pressure to prescribe'

anticholinergics from other members within their healthcare teams, and also the from healthcare professionals themselves, to perform a medical intervention aimed at relieving the symptom of death rattle which could be described as 'The need to do something'.

9.4.3.3 Ethics of administration of anticholinergic agents for the treatment of death rattle.

Within the group discussions, the question of the ethics of administering a drug to a patient, in order to relieve distress in relatives, and the health carers was not raised by the focus group members, or pursued by the facilitator.

The complicating issue of the 'final' injection occurring just before death, should also be considered as an issue both for nursing staff and relatives, whether a 'real' phenomenon or a coincidence.

Further discussion about ethics will be continued in Section 10.2.

10 General Discussion

10.1 Introduction

Data was collected from two hospices on the outcomes of treatment of death rattle with anticholinergic agents. Subjective and objective outcome measures were used. In addition the perceptions of the success of anticholinergic treatment was assessed using qualitative methods with relatives and healthcare professionals to establish whether this mode of treatment was a) effective, b) caused any harm to the patient and c) that the beneficial effects when balanced with the risk of side effects could justify administration of treatment to a patient when the benefit was believed to be for a third party. Ethical considerations formed the basis of the initial research questions for this study. Ethical opinion then continued to impinge upon the progress and direction of the methodology. The main ethical concerns affecting the study were issues surrounding approval of the present study protocol by ethical committees and the problems surrounding consent in this group of palliative care patients.

10.2 Ethics and consent. How this affected the progress of the study

10.2.1 The process of obtaining ethical approval for the present study

The status, function and process of Ethics Committees in regulating the ethical nature of research have changed considerably over the past ten years, and particularly over the last five years, providing a possible explanation for the variable reporting of ethical approval for the studies reviewed in Table 5.1.2.

When embarking on a course of part-time study which was planned to take at least four years to complete, an appreciation of changing ethical requirements was important. Firstly in order to uphold ethical considerations for those patients and healthcare professionals taking part in the present study, but also to ensure that the findings of such work would meet the standards required for

dissemination to the scientific community. In 1999, when the present study was started, the European Directive for research was awaited and was soon to become law.

The delays involved and the hurdles provided by the ethical approval process in 1999, although generally laudable, could be considered to have been an obstruction to the present research project which studied the treatment of death rattle in palliative care. Fourteen months elapsed between the first application to the Multi-Centre Research Ethics Committee (MREC) and receiving final ethical approval from the Local Research Ethics Committee (LREC). The consistency of the decisions made by different Ethical committees could also be questioned as the proposal to use a microphone clipped to patient's clothing was refused for the present study, when a similar study which recruited patients between 1999 and 2001, was given approval for the investigator to apply a mask with an embedded microphone, to the patients face (Wee, 2003). The fact that patient's consent was obtained prospectively was considered a key factor in ethics approval.

The attitudes of MRECs to palliative care research applications were ascertained in a qualitative study (Stevens et al, 2003). The study findings suggested that variability between decisions could be accounted for by the fact that few palliative care study applications were submitted, leading to a lack of experience. The results demonstrated that the main concerns were: (1) the protocol in regard to safeguarding autonomy and justice and (2) with protection of the patient, particularly from intrusion, distress and influence of the researcher. Palliative care patients were also considered to be a particularly vulnerable group. These issues mirror the questions raised by the MREC for the present study. The opportunity for the researcher (CH) to have been present at a discussion of the present study protocol with MREC would have been welcomed. This would have enabled an immediate response in order to address the concerns of the committee and could have facilitated a more streamline process.

There has been much debate over the impact of the European Clinical Trials Directive (2001/20/EC) suggesting that if followed, the new regulations could be particularly damaging to studies designed to assess the effects and the best ways

to use drugs which are already licensed, (Mayor, 2004) such as have been exercised in the present study. The time involved with producing both the supporting data, providing amendments and responses, together with the time taken for the final approval were not insignificant within the course of the present study. The implications for academic research, particularly relevant to pharmacy led studies, which often have short time scales and limited funding, are important with regard to the time required in gaining ethical approval for any trials involving the use of medication in humans (Tully and Cantrill, 2003). Hearnshaw (2004) found variation in the requirements for approval by research ethics committees across Europe. The United Kingdom in particular was considered to have an arduous process for gaining ethical approval. Glaziou and Chalmers (2004) suggested that different approaches to ethics review should be developed for different types of evaluation, taking into account an assessment of the likelihood of potential benefits and harms afforded by the proposed study. This is not to imply that palliative care research requires special ethical guidelines, the arguments for this were refuted by Casarett and Karlawish (2000), but should acknowledge that the risks and benefits of palliative care are difficult to assess. It is hoped that these arguments could be considered in the future, as the ethical procedures in place at the time of the present study, would not facilitate or encourage further research into the treatment of death rattle. The alternative question should be whether it is ethical to continue using treatments where there is little evidence on which to base the risk for benefit against harm in this vulnerable group of patients?

10.2.2 The process of obtaining consent

Consent of several different participant groups was necessary in order to conduct the present study. Consent was required from the patients being recruited into the study and their relatives, those who took part in the carer interviews, and the healthcare professionals taking part in the focus groups. Consent did not pose any problems in the last two groups. However consent of patients into the present study did pose more major problems resulting in recruitment of far fewer patients than was expected.

10.2.2.1 Patient Consent

The problems surrounding the consent of patients in studies involving patients near the end of life, or those too ill to be able to give personal informed consent have been widely debated in the literature and leave many issues still to be resolved, as evidenced by the responses from MREC to this study submission. Following the introduction of The European Clinical trials directive (2001/20/EC), the Central Office for Research Ethics Committees (COREC) produced an information paper covering the statutory requirements for informed consent of participants in clinical trials of investigational medical products (Central Office for Research Ethics Committees, 2004)

Discussion surrounding consent in palliative care studies suggests that one solution to overcome the problem of increasing cognitive impairment compromising the ability of a patient to give informed consent would be to consent the patient on admission, or before their condition had declined (Casarett et al, 2003). This should include a proviso that where a patient's condition is likely to deteriorate, with increasing cognitive impairment, that either re-consent should be considered should the patient regain capacity – or the consent process should involve discussion of the patient's willingness to continue participation if capacity is lost. In practice, our multidisciplinary discussions had arrived at much the same conclusion before the present study started. By definition however, conducting the process of informed consent in the present study would require the patient to comprehend that their condition may deteriorate during their hospice stay to the point where they might require treatment to prevent 'noisy breathing'.

The prospect of obtaining such consent from an anxious patient, perhaps entering the hospice for the first time, who may not have adjusted, accepted or indeed been informed of the full details of their condition, make 'routine' consent for entry into a study of 'death rattle', quite difficult to manage. Casarett (2003) also addressed the possibility of assessing decision-making capacity in this group of patients before consenting, but acknowledged that the process of conducting interviews and scoring this, would be too time consuming. It could also be argued

that such a process would also be unnecessarily intrusive to a patient at this point in their illness.

Rees and Hardy (2003) described a system for advance consent of patients to enter a randomised controlled trial to assess any difference in efficacy between two agents for the treatment of death rattle, work which was published after this study had begun. All patients admitted to the hospital were given a leaflet explaining that research was an integral part of patient care in that institution, giving information of current studies and advising patients that they might be approached about research during their stay. Trial suitability was determined at multi-disciplinary meetings, a method similar to that used in the present study. The patients were primed by the consultant using the terms 'noisy breathing'. This was repeated on each subsequent admission and patients asked to re-sign a consent form on each occasion. The paper does not identify who took consent either initially or on re-admission. Relatives were also involved if the patient was unable to re-sign the consent form. In their initial analysis however, as in the present study, they often found patients too unwell on their first admission to receive the information and give consent. Also more patients than expected were never re-admitted to the hospital and therefore lost to the study.

In contrast to the hospice environments in the present study, Rees and Hardy's (2003) study was carried out in a hospital palliative care environment within a large, well established oncology research unit where nursing staff were accustomed to ongoing research. Nursing culture in the hospice settings in the present study did not seem as open or accustomed to the need for research or may not have been confident in taking part. Many of the aspects of the consent process described by Rees and Hardy (2003) however, were similar to those employed in the present study: Suitable patients were identified at multidisciplinary team meetings or ward rounds with the risk of potential biasing of results by excluding certain types of patients or family groups.

The consent procedure alone however could be the cause of considerable bias in the present study and a considerable number of patients were not consented for

treatment for various reasons. Some patients could not be consented because of poor condition on admission and the lack of time available before treatment needed to be initiated, others because the healthcare team, or doctor felt it was inappropriate and some because staff were just too busy. In some instances it was felt appropriate, with permission from the medical staff, for CH to consent the patient. A further factor observed in the consenting procedure was the difference in palliative care experience of the medical staff who ranged from experienced palliative care specialists and consultants, to more junior doctors on a six month placement. This effect was not observed to be consistent and may require further investigation from the point of view of consenting patients into studies at the end of life. Some junior doctors with less experience of palliative care but perhaps more research experience consented more patients, others approached consent on a much more personal basis. Although this study was not able to quantify or qualify this aspect, it had an effect on the recruitment of patients into the study. One experienced doctor commented that the consent form required signing in several places, which she likened to the most significant paperwork encountered in a life such as a 'mortgage application' which implied an importance above and beyond the intention of the document in this instance.

10.2.2.2 Consent by proxy (legal representative)

When patients were unable to give consent because of illness the option of consent by proxy was used in the present study. The European Union clinical trials directive states on consent with regard to incapacitated adults that:

'3. Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Members States to lay down rules to this effect . Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to a patient, thereby outweighing the risks.....'

' 4. In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients etc inclusion in clinical trials should be on an even more restricted basis. Medicinal products for trial should only be administered to all such individuals where there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.'

(European Union Clinical Trials Directive,2001)

In United Kingdom this has been interpreted under the Medicine for Human Use (Clinical Trials) Regulations, (2004) as:

'The 'legal representative' can not be a person connected with the trial and must be both suitable and willing to act as the legal representative (by virtue of their relationship with the adult) and is available and willing to do so; Or may be the patients doctor, and not connected with the trial, or a similar person nominated by the NHS Trust or Health Board.'

(Central Office for Research Ethics Committees ,2004.)

This route was chosen in the present study, usually when the patient's condition had deteriorated rapidly or when the patient's condition was poor on admission. There is debate surrounding the use of consent by proxy, firstly identifying the proxy. Once identified, how should the proxy then decide whether to enrol a non-competent subject into a study? The question of who should serve as proxy raises several issues. If it is a family member or a close friend, and in some way the proposed research resulted in harm to the patient, then they may subsequently feel some responsibility. The proxy's decision in order to be valid, should be a substituted judgement, that is, what the patient would decide if they could communicate themselves (Karlawish, 2003). However studies have shown that this is not always the case. Warren and co-workers (1986) found that when proxies for a group of 168 patients, in nursing homes, were asked to enrol family members in a minimal risk study, 46% refused on behalf of their patient. Reasons given were that research should not be carried out in such an institution, that the study would disturb the patient and that the proxy would refuse to participate in

the study if asked. However where proxies believed that the patient themselves would have refused consent, 31% of proxies gave consent, in apparent opposition to the patient's wishes.

A further consideration, observed during the present study and from personal experience within the hospice environment, was that even if the patient had been able to give consent, rendering it unnecessary to obtain consent by proxy, feelings of the family and their close involvement with care of the patient, could influence the patient's decisions, particularly if they were in the terminal stages of the disease. If a patient agreed to enter a study, some families may feel aggrieved because it is not what they would have wanted for the patient. Individual family members may disagree, causing unwanted and unnecessary conflict at this time. Some patients may feel a particular loyalty either to the institution or to the staff caring for them who may be conducting the research and this may influence their willingness to cooperate. In the hospice environment, it could be postulated that over a period of time, more likely with a prolonged inpatient stay, complex relationships may be built between doctor and patient. Such a relationship may make the consenting procedure more difficult, this would support the obtaining of consent soon after admission rather than waiting, when a doctor patient relationship may have developed.

Jubb, (2002) emphasised the need to involve the family in the research process, suggesting that the researcher is indeed obliged to obtain informed consent from all family members. However the question remains of how the verbal consent from the relatives would be considered, if full consent had been given from the patient. This raises ethical issues regarding confidentiality and whether it is ethical to extend involvement to all family members.

Karlawish (2003) discussed the issue of consent in end-of life situations in relation to justifying the risks or burdens of the intervention against the benefit that may not be immediately apparent to the participating patient, but could benefit patients in the future. 'Minimal risk' was described as when *'the probability and magnitude of physical or psychological harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or*

during the performance of routine physical or psychological examination or tests.'
(United States Department of Health and Human Services, 2005).

The methodology of the present study did not involve treatment that would differ from generally accepted normal 'current practice' treatment in each of the hospices. However, it was reported by the consenting doctors that when the word 'study' or 'trial' was used during the consent procedure, reassurance was then required for the patient, that the treatment being studied was one which was currently available and regularly administered (with or without formal consent) and that permission was being sought to formally record the outcomes of this treatment to inform practice and disseminate the results.

Many of the discussion papers commenting upon the ethics of research and consent in palliative care focus on Phase I trials for the 'palliative' use of cytotoxic chemotherapy for example (Daugherty et al,1997). The arguments presented in these cases are fundamentally different from the issues facing researchers and patients in addressing symptom control in the last stages of life. Where palliative chemotherapy is offered, the outlook is more hopeful than portrayed in a study measuring effects in the dying phase. Chemotherapy may be promoted as purely palliative (to relieve symptoms rather than prolong life), however the risks may be greater with regard to quality of life and the element of hope remains in the possibility that extension of life may be achieved. Chemotherapy trials also differ in that often new chemical agents are being studied, whereas drugs used in palliative care have often been available for many years for different licensed indications, but lack evidence for efficacy in palliative care treatment.

The situation in the present study, however, was to investigate the use of currently available treatment to alleviate symptoms when there was little 'hope' for the family. The final outcome was inevitable and the aim was to ensure that symptoms were controlled as well as they could be. The motivation for patients and families to enter into such a study are therefore different from palliative studies involving palliative chemotherapy and hinge around the careful discussion of what is possible. The patient's decision to consent may also be coloured by the degree to which they have accepted that the end of life is imminent. The time at

which individual patients and families reach this stage is different for each family unit and between the members in each family unit. This complicates the consent (and indeed the research process as described) procedure further, involving judgment and carefully timed intervention on behalf the researchers and health care workers.

The consent process for dying patients unable to give consent, described by Rees and Hardy (2003) provides an encouraging alternative for future research in palliative care. This is similar to an approach suggested by Jason and Karlawish (2003), namely the use of a research advance directive (RAD). In this system it is proposed that the patient could indicate the type of research that they would or would not participate in, well in advance of incapacity. This general directive could be addressed at an agreed time point at, or after first contact with the palliative care team, introduced as part of the general written information about the hospice service. A general consent form could be compiled, which may then be re-visited prior to entry into a study either by the patient, or assist the legal representative in making a substituted judgment.

Experience gained from the present study, however, has illustrated that in palliative care, there is currently a difference between the health culture of patients being admitted to a teaching hospital for palliative care and those being admitted to a local hospice. In hospital, the patients are likely to have received treatment for their illness and received support from within that unit, prior to needing palliative care which in some units is seamless. Patients often enter the hospice for the first time with the beliefs cultured from past experiences, which colour their expectations, anxieties and fears.

The Mental Capacity Act (2005) which comes into force in April 2007 may clarify issues of consent for treatment, changing the law on proxy decision making, allowing a competent adult to appoint a 'donee' of a lasting power of attorney specifically for medical decisions. Family members (or other appointed donees or deputies) will not have the legal power to consent on behalf of their incompetent relative but the act allows their views on what is in the patient's best interest to be taken into account (Corfield and Granne, 2005).

10.3 Methodology

10.3.1 Gatekeeping and patient recruitment

The small number of patients recruited into the present study was disappointing, as previous work had demonstrated that the required number of patients, could be accessed in the available time period. This premise was confirmed by the number of patients who received anticholinergic drugs but were not recruited into the present study. The literature also reports difficulties in conducting research in palliative care as a reason for the lack of evidence-based treatment (Jubb, 2002). Ethical reasons involving difficulty in obtaining consent in palliative care patients have also been discussed as one reason for poor recruitment (Grande and Todd, 2000).

Attrition due to death, commonly cited as a reason for poor results in palliative care trials was not an issue in the present study as the dying phase was the time period under observation. It became apparent that the study of the dying phase, in relation to measuring the effect of drugs, was a much more sensitive area for the hospice staff to embrace than was apparent during the development phase the present study. Staff consultation and opinion had been sought at all phases of study development and staff had seemed enthusiastic at the opportunity to be involved in the investigation of the treatment of death rattle.

Ling and co-workers (2000) found a relatively high proportion of patients were entered into palliative care trials, but acknowledged that their cancer centre, with a high research profile was not typical of other palliative care centres or hospices. The list of studies in progress during the study period were all of specific palliative therapeutic interventions rather than of the effectiveness of the palliative care service, but none of these involved treatment during the dying phase. Kaasa and De Conno (2001) related their experience in palliative care research, that most patients were receptive to taking part in clinical research. Indeed they supported

patients being allowed the choice to take part in the research, stating that it could be argued to be unethical not to give patients the opportunity to take part.

A previous study reported difficulties in gaining access to patients for a palliative care study in primary care (Ewing et al, 2004). The gatekeeping hurdles identified were not only those of ethics committees, but of practitioner led access, where general practitioners although wanting to be supportive of research, sought to protect patients, expressing concerns about possible anxiety and upset for families. The same gatekeeping issues were described by Daniels and Exley (2001), where home care team nurses were involved in taking consent for patients entering a study to evaluate a new community-based service to be implemented in the terminal stages of the patient's illness. Although the nurses were keen to be involved in the study, they found that their nursing roles conflicted with the consent process, often using their intuition and professional judgment on whether to ask patients to participate. In general nurses have reported it was often easier to gain consent earlier rather than in the later stages of the patients illness (Ling et al, 2000).

10.3.2 Gatekeeping and data collection

Both the quality and quantity of noise monitoring data collected in the present study by the nursing staff during the treatment of death rattle and the number of relatives which were interviewed for their opinions, was also lower than anticipated in the present study. Where reasons were given by nursing staff for not performing the noise monitoring, these usually revolved around problems with the use of the noise meter. Nurses considered that the use of the noise meter was often an unacceptable intrusion when attending relatives who were perceived to be anxious. Subjective scoring of noise levels could be carried out more discretely and indeed these data were available for more patients. However, a significant number of consented patients had no noise monitoring performed and although retrospective data were collected from the medical records for these patients, it was not considered appropriate to include them in the analysis of this study. No specific reasons were given for the lack of data collection. Often there seemed to be difficulty in consistent recording of four-hourly data readings. This could have

been accounted for by staffing levels, the level of patient dependency on the ward, in addition to individual patient situations.

The lack of interviews carried out with the relatives or carers of the patient was also disappointing. However, timing and availability of the researcher to carry out these interviews at times when relatives and patients with death rattle were together in two geographically separate study sites was more of a problem than had been anticipated. This study chose to engage with relatives about the level of distress experienced by both themselves and the patient and their assessment of the benefit of treatment offered at the time this was occurring. This approach was chosen because of doubts expressed about the validity of retrospective assessments by bereaved family members with respect to patient symptoms, including anxiety or distress. Higginson and co-workers, (1994) and Hinton (1996) found similar discrepancies between prospective and retrospective reports of terminal illness by families. Retrospective assessments made by bereaved family members, when compared with evidence available before death, showed that the relative's perception of what the patient wanted or how they felt at the end of life was variable, although this depended on the symptom being reported. The aim of this part of the present study was to discover whether relatives were distressed by the death rattle sound at the time that treatment was being offered. Six of the relatives felt that the noisy breathing contributed a significant amount to their overall distress, but two of these were more concerned about the noise effect on other relatives.

The interviews were not perceived to have caused distress to the relatives who took part in them, the difficulty lay in CH and the relatives being available at a mutually convenient time. It must be recognised that there was always the possibility of bias being introduced to this methodology via gatekeeping, as if relatives had been too distressed to take part in an interview, they would not have been approached.

10.3.4 Other limitations of this study

10.3.4.1 Study design and patient selection.

As previously discussed (Section 4.7), power calculations had indicated that sufficient numbers of patients could be recruited by conducting a combined study in the nine hospices within the West Midlands. Support for this study had been given by the Medical Directors of the Hospices and in anticipation of this, ethical permission was sought from MREC rather than approaching individual LRECs. Although theoretically even a third hospice centre would have provided the required number of patients, had all eligible patients have been consented, entered into the study and monitored, the results from the two hospices have demonstrated that this would have been unlikely. Invitations to the third closest hospice in terms of geographical location to join the study were met with poor enthusiasm by the nursing staff. The length of time taken to move through the Ethics Committee approval system, plus time and resource taken to 'train' the staff of the two hospices involved in the study protocol, made the recruitment of a third centre unrealistic without further resources mainly in terms of support personnel for the study in each hospice. However, the close working relationship and the diversity of communities served by the Hospices within the Region would still offer a viable centre for patient recruitment, if resources were available.

10.3.4.2 The use of a non-randomised observational study to detect the differences in outcome of treatment for death rattle.

The present study sought to introduce a noise meter as an objective measure of the administration of anticholinergic drugs to treat death rattle. Traditional medical models would expect a randomised control trial (RCT) of sufficient power in order to provide results considered to be significant. It was not possible to set up an RCT within the resources available, however the two hospices initially approached had different prescribing regimens in place and it was felt feasible and valid to compare these. The study aimed to add to previous work by introducing an objective

measure of death rattle loudness, in response to interventions and to explore the ethics of this practice using qualitative methods.

The noise meter appeared through the validation study to be a valid method of objectively measuring the loudness of a death rattle noise, and was sufficiently flexible to be used in practice and deemed acceptable by Ethics Committees. The resulting noise meter monitoring data however was limited by the small sample of data collected, in terms of proving or disproving the validity of this method, the combined results from both hospices however showed some correlation with subjective noise scoring. Moreover, the nursing staff were reluctant to use a noise meter, usually when relatives were present, even though it was considered to be unobtrusive. Wee (2003) however, conducted a study in death rattle utilising a mask placed on the face of the patient containing an embedded microphone. Patients were consented prospectively, although repeated monitoring on a regular basis was not carried out. In the current hospice environments it is doubtful whether nursing staff would perform such monitoring on a regular four-hourly basis. It is also unlikely that the Hospice Ethics committees would have sanctioned what appears to be a more obtrusive methodology compared to the methodology used in the present study, as the MREC considered the clipping of a small microphone to patient's clothing to be too obtrusive.

Some patients, particularly those with death rattle lasting longer than a few hours, often presented with fluctuating symptoms with regard to subjective and objective noise levels. Often interventions of drug administration and re-positioning of the patient would occur at the same time, making it impossible to determine which intervention, if any, had resulted in change in death rattle. It was also noted that positioning interventions were sometimes recorded in the patients' medical records but not on the data collection charts.

These observations are important limitations on the data collected during the present study, however they raise the question of the reliability of the data from other studies collected over any period of time under similar circumstances, and question the feasibility of obtaining more reliable data using a randomised

controlled trial methodology alone, even if enough patients were recruited into a trial.

During the literature search, only one study was found which used a randomised placebo controlled approach to study the effect of hysocine hydrobromide against placebo for the treatment of death rattle in palliative care patients. The study was conducted in Austria and had ethical approval, but it was not reported whether the patients were required to give consent. The number of patients recruited was small, and the methodology, as published, leaves some questions unanswered. However in view of the small percentage of patients generally reported to respond to anticholinergic treatment of death rattle, this perhaps challenges the current apparent position on the ethics of conducting a placebo controlled trial on the treatment of death rattle in this group of patients.

Fowell and co-workers (2004) proposed a feasibility study to evaluate different models of research methodology to measure the difference in therapeutic interventions in the use of anti-emetic medication in the dying patient. It may be that the results of this provide some suggestions for carrying such research in dying patients. Alternative approaches to the RCT model for research in palliative have been advocated by Daniels and Exley (2001) and McWhinney and co-workers (1994).

10.3.4.3 Qualitative information: Focus groups to determine opinions of the healthcare professionals.

The focus groups were felt to be successful as far as the aims of this study. Although more focus groups would have been desirable, the themes and opinions expressed by the groups were consistent.

The focus groups in the present study confirmed the general perception, that healthcare professionals believed that death rattle did not usually cause undue distress to the patient. Death rattle was thought by respondents in the focus group to cause distress to relatives, and should be avoided in order to prevent

bereavement issues. Watts and co-workers (1997) conducted a questionnaire amongst a small group of nursing staff and found that nurses perceived that noisy breathing caused distress to all parties but particularly to relatives and implied that nurses felt less confident in the pharmacological management of death rattle using drugs. A lack of pharmacological knowledge amongst the nursing staff was apparent in the present study. The authors (Watts et al, 1997) also detected a lack of confidence in the overall treatment of death rattle and discussed the frustration that nursing staff might feel, faced with an apparent inability to influence the situation. The focus groups in the present study did not highlight any such frustration, although did acknowledge an acceptance that any treatment, pharmacological or non-pharmacological, was not guaranteed to produce the desired effect of relieving death rattle. The balance of beneficial effect versus harm was touched upon but not fully explored. This may have been due to the lack of pharmacological knowledge already described.

There was a strong feeling amongst the nursing staff that information and explanation for patients and relatives, delivered where possible in advance of the symptoms of death rattle occurring, was of great importance in preparing relatives. A difference in approach of nursing staff was identified towards relatives in the inpatient setting, in comparison to the 'home care' environment. Patients cared for at home by their families appeared to receive more pro-active information from their clinical nurse specialists because of the relatively short contact time with healthcare professionals. This raises issues about when, how and by whom this information should be given. The information gained from the focus groups in the present study was generally in line with other literature from palliative care which states that information should be given '*when the patient and or family need to know*' and that the underlying theme should be avoidance of harm (Clayton et al, 2005).

Non-drug treatment for death rattle was acknowledged as a first line intervention by in-patient nursing staff, although they perceived that relatives might have greater confidence in drug treatment prescribed by the doctor, perhaps more so if the drug was given by bolus injection.

Members of all focus groups in the present study expressed the feeling of '*need to do something*' to achieve the aim of a good death or '*deluxe dying*'. It would be useful, using grounded theory, to explore the specific question of the ethical considerations of giving a medication to a patient for the benefit of another with further focus groups of healthcare professionals from a wider area.

10.3.4.4 Qualitative methodology: carer interviews.

The impact of small group size and subsequent data has been discussed together with the merits of conducting interviews at the time of treatment for death rattle versus the practicalities of this process (Section 8.4). Questions have been raised about the validity of retrospective responses of proxies to questions about the patients' distress at the end of life (McPherson and Addington-Hall, 2003) particularly using retrospective methodology. The evidence suggested that proxies can reliably report on quality of services and on observable symptoms but agreement is less likely on more subjective issues such as pain and anxiety. Proxies would have to make a subjective decision about the level of distress that a patient might be in as a result of death rattle, which could imply poor validity when questioned retrospectively. A prospective study compared patients' symptom distress ratings to those perceived by caregivers and physicians in their last week of life (Oi-Ling et al, 2005). Caregivers' ratings agreed well with those of patients for symptoms including dyspnoea, dry mouth, cough constipation and insomnia. Distress due to death rattle could very rarely be rated by the patient themselves but this evidence supports the decision to question relatives about their impressions of the distress caused to the patient by death rattle and the subsequent response to treatment, in a prospective manner. Although this would improve validity, practically this methodology was difficult to achieve in the present study. A short face to face, semi-structured, interview was chosen as being the least intrusive qualitative method for relatives or carers at this time. However it is also acknowledged that the assessment instrument, particularly relating to questionnaires, can cause errors in response, particularly if judgements regarding other peoples' experiences are required (McPherson and Addington-Hall, 2003).

The second aim of questioning the patients' relatives in the present study was to ascertain their level of distress and whether this could be attributed directly to the patient's death rattle symptom, including whether any medication administered to the patient had a positive effect upon the relatives' distress. The prospective methodology was believed to be the most valid way of conducting this for the reasons stated above. Unfortunately the number of relatives interviewed was insufficient to draw any significant conclusions although there was a trend towards more relatives expressing that the death rattle noise caused them distress at the time of the interview.

Nursing staff, during the study focus groups, expressed the belief that the distress experienced by relatives owing to the death rattle could negatively influence their bereavement process. The present study did not aim to explore the effects of bereavement, only distress due to the symptom at the time that the patient was receiving treatment. A retrospective exploration would be required to determine the long term effects of death rattle on bereavement. Wee (2003) as discussed previously, conducted interviews with bereaved relatives of patients who developed death rattle and although some relatives did express that they found the memory of the death rattle distressing, it was concluded that this was not the prime focus of their distress.

10.3.5 Evidence of effectiveness of anticholinergic treatment for death rattle

Although it has already been acknowledged that the numbers of patients recruited in the present study were too small to produce results of statistical significance, certain observations were gathered which assist in the interpretation of previous observational studies, demonstrate areas which require further investigation and question current guidelines.

The results of the present study prompt an exploration of the definition of 'effective' or 'successful' treatment of death rattle. A subjective grading system (in addition to the noise meter recording) for nurses scoring of death rattle noise level, described by Back and co-workers (2001), was employed in this study (Appendix C) providing a standard reference against other studies using a similar

grading system (Morita et al 2004). However, the observations of the pattern of death rattle in the present study indicated that it was frequently variable throughout the patient's dying phase, particularly in those patients with persistent rattle. Previous studies have attempted to measure the effectiveness of anticholinergic drugs in the treatment of death rattle, by classifying the response to treatment in various ways. Noise scores compared at one hour and the final score at death gives no indication of the severity or significance of the noisy breathing over the intermediate period of the dying phase (Back et al, 2001).

Although it is useful to know whether there is a response to the first injection of anticholinergic agent within 30 minutes (Back et al, 2001), (as it would be desirable to control symptoms quickly), this outcome measure does indicate whether the response is sustained or uniform. In addition, the present study demonstrated that nursing staff often perform other care, such as routine repositioning which was not always recorded, even though the information was requested on the data collection chart. It could be argued that the use of single point measurements of noise level is only a valid assessment of the efficacy of the anticholinergic drugs if one can guarantee that this was the only intervention made, and that noise measurements were reliably and frequently recorded. The ultimate conclusion in my opinion is that single point assessments are at best of little value and could be misleading.

The reliability of data collection from any retrospective study are difficult to ascertain and the experience from the present study would imply cautious interpretation of any routinely documented information even when the data is collected in a standard and routine format such as the database arising from the Care of the Dying Pathway (Kass and Ellershaw, 2003). The data from the present study would also imply that in the absence of documenting all interventions (including suctioning and turning), it is not possible to attribute resolution of symptoms to drug treatment alone.

The subjective scoring system used in the present study to assess death rattle noise level has been assumed to indicate a successful level of treatment as assessed by healthcare professionals. (The subjective score sheet on the data

collection chart describes a score of '0' as inaudible, '1' audible only very close to the patient, '2' audible at the end of the bed in a quiet room and '3' clearly audible 20 feet from the bed in a quiet room.) It is assumed that a score of 0 would be the ideal but probably currently not realistically achievable. It is not known what noise level might be an acceptable compromise for the health carers and relatives if we continue to assume that patient's are not distressed by this symptom.

Ellershaw and co-workers (1995) defined death rattle in terms of 'respiratory tract secretions' as the presence of noise 'sounds audible at the bedside'. This definition has been adopted in more recent studies (Morita et al, 2004) incorporating the grading system and assigning 'Grade 3' level death rattle as unacceptable and persistent. The results from a carer interview in the present study (Section 8.3.1) and the corresponding patient profile (Appendix I) indicated that in addition to the actual noise level, the period of time that the relative or carer was exposed to the sound of death rattle may be also be a significant factors in terms of the amount of distress caused. In addition, the quality of the sound and the current anxiety level of attendant relatives and their expectations play a significant role in the distress, leading us to question the validity of a scoring level alone as an outcome measure.

Taking into account the small numbers and limitations in the present study, already discussed, there were some trends apparent when comparing the two types of treatment used first line for the treatment of death rattle at the two hospices. Bolus doses of hyoscine hydrobromide seemed to produce some positive responses in terms of reduction of noise level of death rattle. Continuous infusion with hyoscine butylbromide at the doses administered did not seem to produce as many positive outcomes in terms of reduction of death rattle noise and often further bolus injections were required. These observations need to be placed in context of any additional underlying risk factors for the development of death rattle, most notably, the presence of underlying respiratory infection. The likely benefits of giving an anticholinergic agent to treat death rattle in a patient where there is a possibility of underlying infection should be more carefully considered in terms of benefit for the patient.

There are possible pharmacological and pharmacodynamic explanations for the observations of the different modes of administration, although these are more difficult to interpret because Hospice 1 usually used bolus hyoscine hydrobromide and Hospice 2 favoured hyoscine butylbromide infusion. Bolus doses of injection may have achieved higher plasma levels and therefore been more effective, however the sedative action of the hyoscine hydrobromide may have been significant in reducing the depth of breathing and the possibility of bronchodilation having an effect on the death rattle.

Most of the observational studies carried out in the treatment of death rattle with anticholinergic drugs reported efficacies, depending on the adopted end point, of between 52% and 70% (Table 5.1.2). Agents used, doses and methods of administration varied, making true comparisons difficult to make. Likar and co-workers (2002) published the only randomised placebo controlled trial of hyoscine hydrobromide in the treatment of death rattle, and it would seem that in view of the complexity of each case observed in the present study, that a randomised placebo controlled study could be designed to provide better evidence of the efficacy of anticholinergic drugs to treat death rattle.

Interestingly also, and perhaps still an accepted and therefore unquestioned issue in palliative care, was the lack of awareness shown by nursing staff and some of the registrars in the focus groups of the evidence that was available regarding the use of different anticholinergics to treat death rattle. Published guidelines have acknowledged the lack of evidence base for treatment, questioned the underlying pathology and suggested that differential diagnosis should be considered. Hyoscine (either hydrobromide or butylbromide) was considered by the focus group participants to be first line treatment for death rattle, few of the focus group respondents in this study would have considered using glycopyrronium first line. Although reported to be a potent antisialogogue, glycopyrronium does not appear to have been as effective as anticipated in other studies (Back et al, 2001) although Hughes and co-workers (2000) seemed to find it the most effective of all three agents.

The focus groups expressed an understanding of a cost difference between the anticholinergic agents. The price of a bolus dose of hyoscine hydrobromide 400 micrograms was at the time of the present study was £2.71 compared with £0.80 for 80mg of hyoscine butylbromide. Over 24-hours hyoscine hydrobromide would be six and a half time more expensive than the equivalent dose hyoscine butylbromide. Glycopyrronium was half the price of hyoscine hydrobromide for what was considered to be an equivalent dose. It has been argued that the sedation which occurs as a side effect of hyoscine hydrobromide, resulted in a reduced need for additional sedative drugs when compared with using glycopyrronium. In addition it was considered that the overall expenditure on anticholinergic drugs represented a very small proportion of the overall hospice expenditure on drugs (Back et al, 2001). These findings were questioned by (Murtagh et al, 2002) where a cost saving was achieved by switching from hyoscine hydrobromide to glycopyrronium without an increase in the use of other sedative drugs.

An anticholinergic has been recommended to prevent death rattle in the Care of the Dying Pathway (Ellershaw and Wilkinson, 2003), currently being implemented across England supported by the National Institute for Clinical Excellence (NICE) through their recommendations for Supportive and Palliative Care (NICE, 2004). There is therefore the possibility that patients will routinely be prescribed anticholinergics to treat death rattle, resulting in more patients receiving anticholinergics, to quote one of the focus groups '*the doctor prescribed it therefore we're expected to give it*'. The focus groups showed that although nursing and medical staff were unsure whether the anticholinergics had any effect in treating death rattle, based on experience rather than reading the literature, they were unlikely to question whether it should be given to the patient (apart from one of the medical focus group respondents) if they developed death rattle. The evidence base for this recommended practice supported by NICE should be questioned.

A further question regarding the evidence of whether anticholinergic agents are of benefit to the patient in treating death rattle comes from pharmacodynamic data.

The observed 'onset of action' of hyoscine hydrobromide in relieving death rattle being much quicker than predicted if assuming that the response is due to an antisialogogue action (Bennett, 1996). If the ultimate outcome of reduction in death rattle, relies on drying of secretions, these agents would have little effect on secretions already present. It therefore does not seem logical that an anticholinergic response of reducing death rattle is via this mechanism. It is more likely to be due to a bronchodilatory effect, or perhaps sedation, reducing the respiratory volume. This effect would be expected to be less with glycopyrronium and hyoscine butylbromide. The administration of other sedatives (diamorphine or midazolam) at the same time as anticholinergics was less frequent than expected but did not affect the results significantly in the present study. In other published studies, concomitant medication was not often recorded and accounted for.

Further work is also warranted in the use of prescribing ranges of drug doses which can be administered by the nurses, observing their decision making process on which dose to prescribe, particularly when evidence is lacking as to what the correct dose should be.

10.3.6 Evidence of distress to the patient

Sixty three percent of the relatives questioned in the present study felt that the death rattle distressed the patient, however the sample was small. The focus group respondents tended to believe that distress was not caused to the patient. This remains a difficult question to answer, and will always rely on the comparative subjective views of a proxy. It may be difficult for carers to distinguish between causes of their anxiety and recognise true distress in a patient. It could be argued in this case however, that the general opinion of the healthcare professional may be more reliable than the relative, as particularly in palliative care, signs of distress such as grimacing, restlessness or agitation are particularly closely monitored and attended to.

10.3.7 Evidence of distress to healthcare professionals.

Nursing staff in the ward focus groups particularly, perceived that they needed to be able to 'do something' in an attempt to relieve death rattle in patients, on the basis that this was causing distress, mainly to attending relatives which could be damaging in their bereavement. It was also perceived that medical intervention in terms of medication appeared more 'powerful' in its effect than non-drug interventions. It is a cause for concern that the belief that death rattle will cause distress to the relative is commonly held by healthcare professionals. This belief has now been challenged (Wee, 2003). The nursing focus groups agreed that information and explanation of the death rattle symptom were more actively offered in the community where relatives and carers were likely to be at home caring for the patient with little support, but was less likely to be offered proactively in the ward situation, where one could argue that it might be 'easier to administer an injection'.

10.3.8 Prescribing decisions

The focus groups raised issues about the pressures put upon the palliative healthcare professionals to prescribe drug treatment for death rattle. Medical staff described feeling pressured to prescribe drugs for death rattle, sometimes against their instincts by nursing staff. Nursing staff described feeling pressured to administer anticholinergic drugs to the patient a) because it had been prescribed b) because the relatives asked them to do something. Home Care nursing staff reported asking General Practitioners to prescribe anticholinergics for the patient in their home environment to avoid being challenged by district nursing staff. Home Care nurses in the home situation also experienced pressure from relatives to prescribe '*something to give to the patient*' to appease the relatives anxiety because they feel the need to 'do something'.

This pressure to prescribe anticholinergics was not countered by the expressed lack of confidence from the focus groups, in the perceived effectiveness of anticholinergics for the treatment of death rattle. Most healthcare staff prescribing and those administering the anticholinergic drugs in the focus groups

demonstrated very limited knowledge of the pharmacology and proposed mechanism of action in palliative care, or knowledge of evidence which suggests that other underlying pathology may make the success of treatment with anticholinergics unlikely.

Guidelines and pathways of care, particularly for the care of the dying are intended to ensure that all patients have access to best current treatment. There is however the danger of adopting treatments which do not have a sound evidence base for choice of drug, dosing schedules or routes of administration. This could result in many patients receiving unnecessary medication if those administering the pathways are not fully conversant with current literature, particularly in view of the widespread adoption of the Care of the Dying Pathway (Ellershaw and Wilkinson, 2003) supported by NICE (NICE, 2004).

The occurrence of adverse effects of anticholinergic treatment were not considered to be proportionally represented in the present study. Administration of anticholinergic drugs can cause a number of predictable and well recognised side effects, some of which are used for a positive therapeutic effect. Focus group discussions revealed that the balance of side effects to benefits for the patient was not considered to be a major factor when deciding to administer the anticholinergic. This is important, particularly as the desired outcome was considered to be for the benefit of the attending relatives, rather than the patient themselves.

10.3.9 Ethics and future work.

Ethical considerations have had a vital input upon the present study and warrant further consideration. The methodology although developed in consultation with the hospice staff, to incorporate an objective measurement for sound reduction of death rattle, was not as successful as planned. This was mainly due to ethical and

moral issues together with consent difficulties conflicting with the caring role of the nursing and medical working within the hospice environment. As a result of this, rather than as a result of methodological design failure, recruitment to the present study was low and the quality of the data collected poor. Some trends in the efficacy of death rattle treatment with anticholinergics were seen in that more patients had positive outcomes when treated with bolus injections of hyoscine hydrobromide whereas patient receiving continuous subcutaneous infusions of hyoscine butylbromide did not demonstrate such positive responses overall in terms of reduction of death rattle noise.

Confounding factors in the response to treatment were determined and included the underlying pathologies of the patient, the emotional status of the relatives and carers and the underlying beliefs and ethos of the nursing and medical staff. These confounding factors were often poorly recorded, such as non-drug interventions. This together with the use of outcome measures which may not truly reflect the distress burden of the sound of death rattle make interpretation of previous observational studies on the treatment of death rattle difficult.

The longitudinal database as represented by the Liverpool Care of the Dying Pathway (Ellershaw and Kass, 2003) for which data is continuously collected on treatment, symptoms and variance, is a useful monitoring tool for prospective evaluation of palliative treatment but may be subject to several elements of bias, including the quality of data during the process of ongoing prospective recording. The Pathway encourages prospective prescribing of anticholinergic drugs for patients, in anticipation of them developing death rattle. This prompt introduces the possibility that more patients will receive them, perhaps sometimes when they were not necessary, as healthcare personnel respond to their 'need to do something'.

The problems of research in palliative care have been discussed and reviewed. The use of cluster randomisation has been proposed as a suitable method of randomisation for palliative care research (Fowell et al, 2004). The requirements for patient consent described in this feasibility study are not clear however and it is

felt that the consent procedure may present difficulties in practice. The timing of requesting consent is still a difficult issue even for experienced palliative care staff. It is acknowledged that a centre with an existing culture of ongoing research is likely to be more successful in this respect than in the current environment within most hospices where gatekeeping by the healthcare professionals is common.

10.4 Conclusion

The present study has confirmed that medical and nursing staff generally consider that the main distress caused by death rattle is to the relatives rather than to the patient. In the small sample in the present study 63% of relatives expressed that that death rattle was distressing to the patient that they were attending. Half of relatives interviewed expressed that they had been distressed by the death rattle noise.

Nursing and medical staff were undecided on whether the anticholinergic treatment was effective in treating death rattle. There was a general belief that drug treatment was often not very effective, particularly after a period of time, with some medical professionals perceiving that they did not work at all. Palliative healthcare staff expressed the need to be able to 'do something' to help relatives. The question of whether it was considered to be ethical to administer drugs to the patient (which were not without side effects) in order to achieve this aim was not discussed directly in the present study and should be explored in further work.

The use of a noise meter as a monitoring tool was not well accepted by the nursing staff in the hospice environments as a means of an objective measurement of noise level. When comparing subjective noise scoring with noise meter readings some inconsistencies were noted although there was a correlation between the resulting objective and subjective noise scores. It is not clear whether this was a real effect, artefactual or whether the human perception and reaction to the noise of death rattle is more complex than is capable of being measured in decibels by a noise meter. Based on the results of the present study, it is thought

that the noise meter could be a useful monitoring tool, but data collectors would need to be more comfortable using it in the environment of the dying patient.

There was no evidence from the responses of patients in the present study that hyoscine butylbromide by infusion or the administration of glycopyrronium produced a consistent reduction in death rattle noise, although some positive responses were seen after bolus administration of hyoscine hydrobromide.

Taking account of the pharmacology of the anticholinergic drugs and the proposed speed of response from the hyoscine hydrobromide in the present study, reinforces Bennett's (1996) observation that the immediate effect seen in patients that respond to hyoscine hydrobromide is more likely to be due to depression of ventilation and a degree of bronchodilation rather than inhibiting salivary secretions. In persistent or 'type 2 death rattle', anticholinergic agents are therefore unlikely to produce a reduction in death rattle.

The available literature on death rattle in palliative care does not seem to be well known, as illustrated by the focus groups, and should be included in more detail in palliative care education, including the differential diagnosis of death rattle and bronchorrhea where alternative pharmacological approach may be more appropriate. This information should also be passed on to the carers and relatives in a positive and proactive manner both in the inpatient and home care environment.

10.5 Further work

Further work to study the success of drug treatment of death rattle should follow a randomised placebo controlled trial methodology, perhaps using the cluster randomisation and an advanced consent procedure in order to provide evidence that anticholinergic drugs are effective in the treatment of death rattle. Outcome measures should include consideration of data collection which accounts for death rattle occurring throughout the patients dying phase, rather than utilising single point measures. There should also be research into a method of accounting

for the action of concomitant medication administration on death rattle. Further work is also required to explore the trend found in the present study, that continuous infusions of hyoscine butylbromide did not seem as effective as bolus doses of hyoscine hydrobromide.

In view of the poor evidence of the effectiveness of anticholinergic drugs for the treatment of death rattle and the postulated underlying reasons for the cause of 'type 1' and 'type 2' death rattle, further exploration of the views of relatives and carers is warranted, to determine whether they would agree to the patient receiving treatment for this symptom, if consensus was that death rattle did not cause distress to a patient who was not fully conscious. Further work should also consider developing more active support to help those relatives who feel distress, to cope with this and move away from treatment by proxy.

Before we commend anticholinergic therapy to our general guidelines in palliative care for the treatment of death rattle, we need to be sure we are doing it for the right reasons.

The final two quotes are contributions taken from the focus group discussion, which seem to embrace a further dimension in the palliative treatment of death rattle. The quotes reflect back to the most important question of whether administering drugs to the patient for the perceived benefit of a third party is indeed an ethical practice that can continue to be defended.

Specialist registrar group D *'Which also comes back down to well, does it actually work? Or is it just what everybody thinks works that matters?'*

Specialist registrar group D *'... And its almost like your colleague was making a contrast between a situation where she actually, definitely wanted to do something that she knew was going to be effective, rather than do something that we probably all do a bit, for other reasons.'*

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Appendix A

To establish Multi-Centre Research Ethics Committee (MREC) Application Form

Full title: MREC response February 2000

To establish best practice in the provision of analgesia in palliative care patients
MREC Ethical Approval letter

Principal investigator (who will be responsible for posting data to the MREC)

Name: [Faint text]
Address: [Faint text]
City: [Faint text]
Postcode: [Faint text]
Telephone: [Faint text]
Mobile: [Faint text]

Employed by: [Faint text]
Job title: [Faint text]
Institution: [Faint text]
Address: [Faint text]
City: [Faint text]
Postcode: [Faint text]
Telephone: [Faint text]
Mobile: 0976 563 220

Signature: [Faint text]
Date: [Faint text]



Aston University

Content has been removed due to copyright restrictions

This section must be completed fully. A copy of the protocol should be enclosed with the application form, but it is not sufficient to complete questions by referring to the protocol.

9. Aims and objectives of project (Approx. 250 words)

Aims: The aims of the proposed project are to establish, implement and evaluate the optimal guidelines for the use of anticholinergic medications that may be used to relieve the adverse effects of excessive pharyngo-tracheal secretions in terminally ill patients receiving palliative care.

Objectives:

1. To undertake a systematic international review of the evidence-base supporting antisecretory treatments used within palliative care.
2. To develop and validate a practical method to assess distressing pharyngo-tracheal secretions in patients receiving palliative care.
3. To undertake an evaluation of the efficacy of the principal antisecretory treatment regimens used currently in 9 in-patient hospice units within the West Midlands Region.
4. To establish and compare current practice in antisecretory therapy within the UK by use of self-completion postal questionnaire directed to those responsible for care in the hospices.
5. To develop guidelines for antisecretory therapy based upon cost-effectiveness analysis.
6. To assess the results of implementing guidelines for antisecretory therapy through audit of resultant changes in practice.

10. Scientific background of study (Approx. 250 words)

The prevention or treatment of distressing pharyngo-tracheal secretions in the dying patient is of considerable importance. In a normal person, these secretions would cause initiation of the cough and swallowing reflex. However a patient who is in the last phase of terminal disease is often unable to respond in this manner owing to profound weakness or semi-consciousness. The inability of the patient to clear bronchial and oral secretions may cause greater distress to relatives, nurses and medical staff than the patient. Carers who accompany their dying relative often endure the sound of the "death-rattle" which is a graphic memory that exacerbates the trauma of bereavement.

The actual cause of "death-rattle" is unknown but may have several aetiologies. The principal drug treatment is subcutaneous administration of anticholinergic agents, hyoscine hydrobromide, hyoscine butylbromide or glycopyrronium. However in the 9 West Midlands in-patient hospices, there are at least 5 different approaches to the management of excess respiratory secretions. Estimates of the projected costs of using each of these treatments throughout the WM varies 4 fold, ranging from £29,123 to £129,599 depending on the regimen chosen.

In summary, there appears to be variation in the treatment of this common and distressing symptom in dying patients with little data available on the comparative efficacy with which to develop an effective management strategy. There are however, recognised difficulties in conducting traditional randomised controlled clinical trials in this group of patients.

The proposed study will document variations in antisecretory therapy, compile evidence to assess the relative efficacy of each recorded strategy, produce guidelines for optimal treatment and evaluate any benefits of these recommendations once implemented.

11. Brief outline of project (Approx. 250 words)

Owing to the ethical and methodological problems associated with employing a placebo randomised controlled trial in this sphere of practice, the plan of investigation is as follows:

1. To undertake a systematic review of peer assessed literature in order to determine the nature and extent of evidence supporting the range of therapy choices in existence.
2. To pilot, evaluate and validate a method of secretion assessment. The method will include counting respiratory rattles per minute and the associated respiratory rate using a stethoscope placed over the trachea. To obtain a "rattle index" = rattle rate min⁻¹ /Respiratory rate min⁻¹
3. To evaluate over a period of 18 months the efficacy of antisecretory regimens used within the 9 inpatient hospices in the West Midlands Region. This will involve identification of patients receiving treatment for accumulation of large airway and tracheo-pharyngeal secretions by hospice staff according to protocol directions. The collection of data (byCH) including antisecretory agent prescribed, concomitant medication, doses, routes(s) of administration, duration of treatment, documented symptom response, diagnosis and any adverse drug events by review of patient medication and medical records. The assessment of response to antisecretory treatment by recording the "rattle index" on a response to treatment from that includes an indication of the patients level of consciousness at the time of measurement. This will involve input from the nursing staff. It is proposed that response to treatment on a subjective level will be asked of carers or relatives who may be in attendance. This would involve a short questionnaire with tick box responses from professional carers. For relatives, a short one to one verbal structured interview would be conducted to record their assessment of the severity of the problem and outcome of treatment by asking how much they thought it had improved e.g. "no change", a "bit better", "much better". All data will be anonymised and entered into a relational database to be analysed according to the prescribed drug regimen.
4. Self-completion postal questionnaires will be sent to all Hospice Medical directors in the UK identified through the Hospice Directory 1999 in order to establish comparative current practice outside the West Midlands.
5. A cost-effectiveness profile associated with each antisecretory treatment regimens used within the West Midlands will be established.
6. The results of the survey of drugs will be presented to representative specialists to formulate a protocol based on the evidence gained from questionnaires, literature and current practice in the West Midlands using a Delphi Group approach.
7. Protocols will be produced in hard copy and disseminated by post. with the study findings will also be presented by seminar. Re-evaluation of practice will be carried out after a 3-month test period in order to determine the effects of guideline implementation.

12. Study design (e.g. RCT, cohort, case control, epidemiological analysis)

Cohort

13. Size of the study (including controls)

Will the study involve:

(a) Human Subjects Yes No

i) How many patients will be recruited?

250 patients minimum

ii) How many controls will be recruited? N/A Cohort Study

iii) **What is the primary end point?** Effectiveness of antisecretory regimen in reducing respiratory rattle

iv) **How was the size of the study determined?**

Power calculations – estimation of population parameters

v) **What is the statistical power of the study?**
0.95

(b) **Patient Records** *Yes* *No*

i) **How many records will be examined?**

A minimum of 250 records, one set of records for each patient entered into the study.

ii) **How many control records will be examined?** *N/A Cohort Study*

iii) **What is the primary end point?** *N/A*

iv) **How was the size of the study determined?** *N/A*

v) **What is the statistical power of the study?** *N/A*

14. Scientific critique

Has the protocol been subject to scientific critique? If so, please give the following information:

If the critique formed part of the process of obtaining funding, please give the name and address of the funding organisation:

The project has been submitted for NHSE New Blood Fellowship. Outcome is awaited

If the critique took place as part of an internal process, please give brief details:

The project proposal has been reviewed informally by Janet Dunn, statistician at the Cancer Research Unit, Queen Elizabeth Hospital, Birmingham. Project proposal has also been presented to Specialist Palliative Care Clinicians at the West Midlands Regional Palliative Care Physicians Meeting.

If no critique has taken place, please explain why, and offer justification for this:

15. How will the subjects in the study be:

i) selected?

All patients receiving anticholinergic treatment for the management of "chest rattle" in the hospice.

ii) recruited?

Recruitment will be undertaken by the nursing, medical, or pharmacy staff caring for the patient

iii) what inclusion criteria will be used? All patients requiring anticholinergic therapy for the treatment of pharyngo-tracheal secretions.

iv) what exclusion criteria will be used? Patients receiving anticholinergic therapy for reasons other than excess pharyngo-tracheal secretions.

16. How will the control subjects group (if used) be:

(Type N/A if no controls)

N/A

i) selected?

ii) recruited?

iii) what inclusion criteria will be used?

iv) what exclusion criteria will be used?

17. Will there be payment to research subjects of any sort?

Yes No ✓

If yes, how much per subject and for what?

18. Is *written* consent to be obtained?

✓ Yes No

If yes, please attach a copy of the consent form to be used.

If no written consent is to be obtained, please justify.

A written consent form has been produced for completion by the patient or relative, however as this study evaluates the outcome of usual practice, and noting the fact that a high proportion of patients may not be capable of making informed consent which is a distressing time for relatives, feedback from the Ethics Committee would be appreciated on whether completion of a consent form is required for all cases.

19. How long will the subject have to decide whether to take part in the study?

If less than 24 hours please justify.

This study will record the outcome of practice which is initiated to provide symptom control for a patient in the last few days of life. It would be inappropriate to withhold treatment outwith normal practice.

20. Please attach a copy of the written information sheet or letter to be given to the subject.

(See Guidelines page 3 and Appendix A.)

If no Information Sheet is to be given, please justify.

21. Have any special arrangements been made for subjects for whom English is not a first language?

Yes No N/A

If yes, give details.

Current arrangements in hospices will cover these circumstances.

If no, please justify.

22. Will any of the subjects or controls be from one of the following vulnerable groups?

Children under 18 (16 in Scotland)

People with learning difficulties

Unconscious or severely ill

Other vulnerable groups e.g. mental illness, dementia

✓Yes No

If yes, please specify and justify:

By the nature of the project, these patients will be in the last days of life and a large proportion will be severely ill or unconscious. It is important to evaluate the treatment that these patients receive in view of the variation around the Region, the lack of peer reviewed evidence to support the effectiveness of the treatments for the patients or carers of the patient.

23. What special arrangements have been made to deal with the issues of consent for the subjects above? (Please see Guidelines.)

An information sheet and consent form has been produced which should be signed by the patient or relative.

24. Does the study involve the use of a new medicinal product or medical device, or the use of an existing product outside the terms of its product licence? (Please see Guidelines.)

Yes No ✓

If yes, please complete Annexe A of the Application Form.

25. Will any ionising or radioactive substances or X-Rays be administered? Yes No ✓

(NB Please ensure information in Question 14 includes exclusion criteria with regard to ionising radiation if appropriate.)

If yes, please complete Annexe B of the Application Form.

26. Please list those procedures in the study to which subjects will be exposed indicating those which will be part of normal care and those that will be additional (e.g. taking more samples than would otherwise be necessary). Please also indicate where treatment is withheld as a result of taking part in the project.

In order to pilot and validate a method of quantitative assessment of the effect of antisecretory therapy it is proposed to measure a "rattle index". This will involve the placement of a stethoscope over the trachea of the patient and counting audible rattles per respiration over a minute. Although a stethoscope would be used to listen to the chest, it is not normal procedure to count for a minute. It is not anticipated that this will cause any distress to the patient. The view of carers on any effects of treatment would not normally be formally recorded apart from existing nursing or medical notes.

27. Are there any potential hazards?

Yes No ✓

If yes, please give details, and give the likelihood and details of precautions taken to meet them, and arrangements to deal with adverse events.

The only hazard would be those associated with the usual side effects of anticholinergics e.g. dry mouth, blurred vision, urinary retention and confusion. As this study is observing normal hospice practice, these adverse effects would be recorded and documented.

28. Is this study likely to cause any discomfort or distress?

Yes No ✓

If yes, please give details and justify.

Palliative therapy aims to relieve discomfort and distress in the patient and family where there is no further curative therapy. This study aims to carefully document current practice to evaluate any difference in the variation in treatment around the Region. It is possible that discussing clinical uncertainty (i.e. that it is not clear which, if any, antisecretory treatment is the best) with carers and patients may provoke some distress. The process of consent therefore requires great sensitivity and those involved in it will receive training from the researcher.

29. What particular ethical problems or considerations do you consider to be important or difficult with the proposed study?

Please give details.

As this study is proposing to study the effectiveness of current practice which is variable and has a minimal evidence base, the most important ethical consideration would be the consequences of not carrying out such studies in palliative care. The issues surrounding informed consent are large. Often consent will be given by the carer as the patient will be too unwell. Both the carer and the patient are extremely vulnerable at this time in their lives and may have difficulty in absorbing the information, seeing the issues of clinical uncertainty in perspective and not being frightened by it. Making any decision can be very burdensome at this time. The skill of the consentor is of key ethical importance. Ethical considerations impose restrictions on methodology which raise challenges to ensure that outcomes can be clearly defined and the aims of the study achieved.

30. Will information be given to the patient's General Practitioner?

Yes No

Please note: permission should always be sought from research subjects before doing this.

If yes, please enclose an information sheet/letter for the GP.

If no, please justify:

The study is observing the effect of treatment that would be given as normal practice for symptom control in the Hospice.

31. If the study is on hospital patients, will consent of all consultants whose patients are involved in this research be sought?

Yes No

N/A

If no, please justify:

Product liability and consumer protection legislation make the supplier and producer (manufacturer) or any person changing the nature of a substance, e.g. by dilution, strictly liable for any harm resulting from a consumer's (subject or patient) use of a licensed product.

32. Have arrangements been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, a subject for non negligent harm?

(Please indicate N/A if not applicable)

Yes No N/A

If yes, please give details of compensation arrangements with this application.

For NHS-sponsored research, HSG(96)48 reference no. 2 refers.

For pharmaceutical company sponsored research, the company should confirm that it will abide by the most recent ABPI guidelines (*Manual V.14.1.1*)

33. In cases of equipment or medical devices, have appropriate arrangements been made with the manufacturer to provide indemnity?

(Please indicate N/A if not applicable)

Yes No N/A

If yes, please give details and enclose a copy of the relevant correspondence with this application.

34. Will the study include the use of any of the following?

Audio/video recording

Yes No ✓

Observation of patients

✓ Yes No

If yes to either:

- i) How are confidentiality and anonymity to be ensured?

All data will be collected on forms with identification of initials and hospice number. This will allow the researcher to access the appropriate patient records. Although all data will be entered into a computer program for analysis, no names will be recorded. Anonymised numbers will be assigned, the code to which will be held by the researcher(CH).

- ii) What arrangements have been made to obtain consent for these procedures?

Consent will be requested on the enclosed consent form.

35. Will medical records be examined by research worker(s) outside the employment of the NHS?

Declarative

Yes No

If yes, please see Guidelines.

In so far that some of the hospices involved are charitable Trusts rather than NHS institutions. Although the researcher is currently employed within the NHS, funding sources may change e.g. to come from the Hospice.

36. What steps will be taken to safeguard confidentiality of personal records?

Confidentiality will be maintained, as is normal practice. Only the researcher (CH) will have access to any link from codes back to patient names, record numbers. At no time will this data be available to anyone except the researcher and will not be divulged in any way.

37. What steps will be taken to safeguard the information relating to specimens and the specimens themselves?

N/A

PLEASE ENSURE THAT YOU COMPLETE THE CHECKLIST ON THE FRONT COVER OF THE APPLICATION FORM AND ENCLOSE ALL RELEVANT ADDITIONAL DOCUMENTS.

DECLARATION

The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

I understand it is my responsibility to obtain management approval where appropriate from the relevant NHS body before the project takes place.

I agree to supply interim and final reports on the pro forma provided, and to advise my sponsor, the MREC from which approval was granted for this proposal and any local researchers taking part in the project of any adverse or unexpected events that may occur during this project.

Signature of Principal Researcher:

Date:.....

This form is to be used if the study involves the use of a new medical product or medical device, or the use of an existing product outside the terms of its produce licence.

- i) Is a pharmaceutical or other commercial company arranging this trial? *Yes* *No*
 If no, has approval of the licensing authority been obtained by means of a DDX? *Yes* *No*

- ii) Does the drug(s) or device have a product licence(s) for the purpose for which it is to be used? *Yes* *No*
 If yes, please attach data sheet or equivalent.

- iii) Is any drug or medical device being supplied by a company with a Clinical Trial Certificate or Clinical Trial Exemption? *Yes* *No*
 Please attach CTC, CTX, or DDX.

- iv) Has a CTC, CTX or DDX been applied for but not yet received? *Yes* *No*
 If so, the application can be made but a valid CTX must be provided to the MREC before the research can proceed

- v) Details of drugs to be used (Please complete the table below for each drug making additional copies of this page as necessary)

Approved Name(s):

Hyoscine hydrobromide (Scopolamine hydrobromide)

Generic Name:

Hyoscine hydrobromide (Scopolamine hydrobromide)

Trade Name:

Non-proprietary injection, Scopoderm Patch TTS

<u>Strength</u>	<u>Dosage and Frequency</u>	<u>Route</u>	<u>Duration of Course</u>
400 microgram/ml	400 micrograms	Subcutaneous injection	When required
400 micrograms/ml	0.6 – 2.4mg	Subcutaneous infusion	Over 24 hours
1mg /72 hours	1mg/ 72 hours	Transdermal patch	As required

Approved Name(s):

Hyoscine butylbromide

Generic Name:

Hyoscine butylbromide

Trade Name:

Buscopan

<u>Strength</u>	<u>Dosage and Frequency</u>	<u>Route</u>	<u>Duration of Course</u>
20mg/ ml	20 -180mg	Subcutaneous infusion	Over 24 hours
	20-40mg	Subcutaneous injection	When required

Approved Name(s):

Glycopyrroium bromide

Generic Name:

Glycopyrronium bromide

Robinul

Trade Name:

<u>Strength</u>	<u>Dosage and Frequency</u>	<u>Route</u>	<u>Duration of Course</u>
200 micrograms/ ml	0.16 – 1.2mg	Subcutaneous infusion	Over 24 hours
	200 – 400 microgram	Subcutaneous injection	When required

Although none of these agents have a product licence for subcutaneous administration or use in palliative care, the use of these agents in this way for the palliative treatment of excessive bronchial secretions is accepted good practice. All of these agents are included in the BNF under Prescribing in Palliative Care.

- vi) **When Drugs not listed in the British National Formulary are being used, applicants should provide the following information on not more than 3 sides of A4 paper :**
- a) **What is the formulation, purity and source of the Drug ?**
 - b) **What are the pharmacological actions of the Drug - including those not relevant to the proposed therapeutic indications ?**
 - c) **Toxicology - including details of species, number of animals, doses, duration of treatment and route(s) of administration. Important findings should be summarised.**

d) Clinical pharmacology in Man including :

- Extent of Use in Man
- Dosage schedules used - dose, route, duration
- Side effects and their frequency
- Information on duration of action and mechanism of elimination, if known.

e) Applicant's experience with this drug in man. Give brief information on previous studies, number and type of subjects and nature and incidence of side effects.

vi) Details of Medical Device

vii) If an electrical device, has the device been through acceptance and safety testing?

Yes No

Give details:

This form is to be used if the study involves the use of additional ionising or radioactive substances or X-Rays.

a) **RADIOACTIVE SUBSTANCES**

i) **Details of substances to be administered** *(Please complete the table below)*

Investigation:

Radionuclide

Chemical form

<u>Quantity of radio-activity to be administered (MBq)</u>	<u>Route</u>	<u>Frequency</u>
--	--------------	------------------

ii) **Estimated Effective Dose (Effective Dose Equivalent) (mSv):**
(Please supply source of reference or attach calculation)

iii) **Absorbed dose to organ or tissues concentrating radioactivity (mGy)**
(Specify dose and organ)
(Please supply source of reference or attach calculation)

b) **X-RAYS**

i) **Details of radiographic procedures**

<u>Investigation</u>	<u>Organ(s)</u>	<u>Frequency</u>
----------------------	-----------------	------------------

ii) **Estimated Effective Dose (Effective Dose Equivalent) (mSv):**

(Please supply source of reference or attach calculation)

**MULTI-CENTRE RESEARCH ETHICS COMMITTEE FOR
WEST MIDLANDS REGION**

MREC RESPONSE FORM

Application reference number: MREC/00/7/06
(please quote on all correspondence)

Your application has been considered under the following headings and the MREC would like to make these comments:

DETAILS OF APPLICANT *(Section 1)*

(1) Principal Investigator :

Name	Mrs Christine Hirsch
Qualifications	BPharm, MSc, MRPharmS, MCPP, AddipClinPharmT
Address of Principal Investigator	Pharmacy Department Queen Elizabeth Hospital University Hospital Birmingham NHS Trust Edgbaston Birmingham B15 2TH
Title of Project	To establish best practice prescribing of anticholinergics in palliative care
Name and Address of Sponsor	

DETAILS OF PROJECT (Section 2)

(2) Scientific Value and Validity of the Proposal

- ✓ a) Clarification is required regarding why the drug is given to the patient and whether they receive any benefit from it, or whether it is given mainly to decrease distress for relatives.
- ✓ b) Statistical Analysis - further detail is requested, e.g., an estimate of what reduction of the rattle index might be worth achieving with drug therapy. An estimate of the differences between drugs which may be thought to be worthwhile.
- c) Committee felt that the side effects of the drugs could be distressing. It was questioned whether information on side effects will be obtained (some are potentially serious, e.g., parotitis from a dry mouth).
- d) It was suggested that as the death rattle is relatively loud, it could be discreetly monitored by a nurse without placing a stethoscope on the patient. This would cause less disturbance for the patient.

RECRUITMENT, INTERVENTION, RISKS AND ETHICAL PROBLEMS

(Sections 3, 5 and 6)

(3) Welfare of the Research Subject

- (i) Hazards, discomfort, distress

CONSENT (Section 4)

(4) Consent of the Research Subject

- a) It was felt that the additional burden to the patient was minimal and that consent may not be necessary. The final decision on this aspect has been deferred for further consideration.
- b) It was questioned whether consent could be obtained prior to the patient becoming semi-conscious/unconscious and clarification of this is sought.
- c) Committee would prefer that consent is obtained from the carers before they complete the questionnaires. It was felt that the questionnaires were helpful and may give the carer a sense of satisfaction to be included in the patient's care. The Chairman will seek clarification from the independent reviewer regarding this.

INDEMNITY and CONFIDENTIALITY (Section 7)

(5) Confidentiality

(6) Indemnity

GENERAL COMMENTS

Patient Information Sheet

- a) The patient information sheet to the carer indicates that the number of rattles will be counted, but there is no indication that the stethoscope will be placed on the windpipe (but see point 'g' above).
- b) As the researcher is looking at the patients notes, there should be an indication that the researcher is a professional pharmacist and whether the study is being done as part of the researcher's thesis.
- c) The questionnaires should be submitted for review.

Review by the MREC:

The following items have been reviewed in connection with the above study to be conducted by the investigator: (tick as appropriate)

- | | |
|--|--|
| Protocol (✓) | Provision for compensation/treatment of subjects (✓) |
| Protocol amendments () | Compensation for subjects participation (✓) |
| Methods of initial recruitment to study (✓) | Subject information sheet (✓) |
| Compensation for investigators participation () | Subject consent form (✓) |

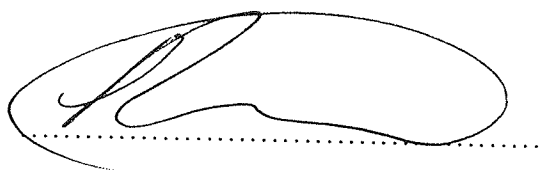
Application reference number: MREC/00/7/06

Your application has been:

- (a) Approved
- (b) **Deferred subject to review by Committee of the points highlighted overleaf**
- (c) Rejected (additional comments if appropriate)

Date of Review: 24th February 2000

Signature of Chairman or Representative:



Name Dr R.D.S. Watson

PLEASE NOTE:

- i) no research subject is to be admitted into the trial until approval has been obtained from the appropriate research ethics committees;
- ii) no significant changes to the research protocol should be made without appropriate research ethics committee/chairman's approval;
- iii) you must promptly inform the MREC and appropriate LRECs of deviations from or changes to the protocol which are made to eliminate immediate hazards to the research subjects; of any changes that increase the risk to subjects and/or affect significantly the conduct of the research; all adverse drug reactions that are both serious and unexpected; new information that may adversely affect the safety of the subjects or the conduct of the trial;
- iv) you must complete and send to the MREC the attached progress report form once a year, and the attached Final Report Data Collection Form when your research is completed.

It is important that you retain the original of this response form as you will be required, if you are successful in obtaining MREC approval, to enclose a copy along with other documents to any local researcher who is going to participate in the projects in future.

**MULTI-CENTRE RESEARCH ETHICS COMMITTEE
WEST MIDLANDS REGION**

Chair: Dr R. Watson
Administrator: Maureen Thrupp

Mrs Christine Hirsch
Pharmacy Department
Queen Elizabeth Hospital
University Hospital Birmingham NHS Trust
Edgbaston
Birmingham B15 2TH

Birmingham Health Authority
Directorate of Public Health
St Chad's Court
213 Hagley Road
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Birmingham
B16 9RG

Tel: 0121 695 2382
Fax: 0121 695 2233

2 October 2000

Dear Mrs Hirsch

Research Protocol: MREC/00/7/06 - To establish best practice prescribing of anticholinergics in palliative care

Paperwork Approved:

- Patient Information Sheet, dated September 2000
- Patient Consent Form, dated December 1999
- MREC Application Form, dated 17th January 2000
- Questionnaire, dated March 2000
- Protocol, dated December 1999

The West Midlands MREC reviewed your application on 24th February 2000. The members of the Committee present agreed that there is no objection on ethical grounds to the proposed study whose title is given at the head of this letter. I am, therefore, happy to give you our approval on the understanding that you will follow the protocol as agreed. Any comments the MREC wished to make are contained in the attached MREC Response Form. The project must be started within three years of the date on which MREC approval is given. I would ask you to submit to LRECs only the revised paperwork reflecting the requirements of the MREC as referenced in the response form.

Please read the notes regarding notification of changes and completion of progress reports at the end of the Response Form carefully, as the MREC requires that they be followed. In addition approval is given subject to the conditions set out below:

Conditions of Approval

- You follow the protocol agreed and advise the MREC of any changes made. Any changes to the protocol will require prior MREC approval.
- You complete the final report form sent to you at the end of your project and return it to the MREC Administrator

- You notify any serious unexpected adverse drug reactions to the MREC Administrator, appropriate LRECs and your sponsor using the procedure set out in the General Guidance for Researchers

You will no doubt realise that whilst the MREC has given approval for the study on ethical grounds, it is still necessary for you to obtain management approval from the relevant Clinical

Directors and/or Chief Executive of the Trusts (or Health Boards/DHAs) in which the work will be done.

Local Submissions

It is also your responsibility to ensure that any local researcher seeks the approval of the relevant LREC before starting their research. To do this you should submit the appropriate number of copies of the following to the relevant LRECs:

- this letter
- the MREC Application Form (including copies of any questionnaires)
- the attached MREC response form
- Annexe D of the Application Form
- **one** copy of the protocol

It is important to check with the respective LRECs the precise numbers of copies required as this will vary and failure to supply sufficient copies could lead to a delay.

The Local Researcher is also responsible for obtaining management approval from the relevant NHS body (Acute Services or Primary Care Trust) before recruitment to the research starts.

Local Sites

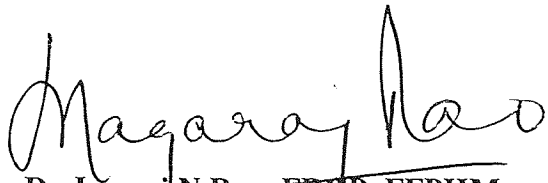
Whilst the MREC would like as much information as possible about local sites at the time you apply for ethical approval it is understood that this is not always possible. You are asked, however, to send a completed copy of Annexe C for each local site as soon as a researcher has been recruited. This is essential to enable the MREC to monitor the research it approves and to the smooth running of the evaluation.

ICH GCP Compliance

The MRECs are fully compliant with the International Committee on Harmonisation/Good Clinical Practice (ICH) Guidelines for the Conduct of Trials Involving the Participation of Human Subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Constitution, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997. The Standing Orders and a Statement of Compliance were included on the

computer disk containing the guidelines and application form and are available on request or on the Internet at <http://dSPACE.dial.pipex.com/mrec>

Yours sincerely

A handwritten signature in black ink, appearing to read 'Jammi N Rao', written in a cursive style.

Dr Jammi N Rao, FRCP, FFPHM
Chairman, MREC West Midlands

Enclosures Composition of Members

Committee Members in Attendance:

Dr Rob Watson, Chair
Dr Donald Portsmouth
Dr Jawad Sheihk
Dr Chris Birt
Dr Kate Tunna
Dr Heather Draper
Mr Nigel Ballantine
Mr Timothy James
Professor Gilbert MacKenzie
Mrs Pat Moseley
Ms Debra Easlea
Ms Christiane Neumann

Appendix B

Patient information sheet

Patient consent form

Comparing the treatments currently used in Hospices to treat "throat rattles"

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or you would like more information.

What is the purpose of the study?

People who are very ill sometimes have problems clearing mucus or phlegm from their throat because they are not able to cough well. This causes a rattling sound as they breath in and out. It can occasionally be troublesome to the patient but usually they themselves are unaware of it. Sometimes the rattling noise can be distressing to those sitting with the patient.

To help prevent this problem, doctors may prescribe one of three drugs which help to dry up the mucus. These are two types of hyoscine and another drug called glycopyrronium bromide. All three drugs are in common use by Hospices and care staff around the country.

In order to find out if any one of these drugs is any better than the others in relieving the "throat rattle" we would like to record your opinion (as the patient or the carer or relative) on how well the treatment which is used in your hospice worked. It should be stressed that there has been no change from the treatment usually used in this hospice and taking part in this study will not in any way affect the treatment you receive.

You, or the patient you are caring for has been prescribed drugs to relieve "throat rattle". We are seeking your permission to allow us to record the response of the patient to the treatment. This does not involve any tests other than the use of a noise meter held 2 feet away from the patient. Do you have any objections to the observations taking place? We should also value your opinion on the effectiveness of the treatment by asking you some questions.

Information about other medicines and treatments that the patient has together with the diagnosis of their illness will be noted from the medical notes. All information will be recorded anonymously. The results from the study will not use individual patient's names. The researcher is a professional pharmacist and the study will form part of a thesis for a doctorate (PhD) research degree.

We think that the information we collect may help to improve the way that "throat rattles" are treated in the future.

Involvement in this research project is voluntary. You may decide not to allow details to be recorded. A decision not to participate will not in any way affect the treatment which you or the person you are caring for receives.

If you require any further information, please ask one of the hospice doctors. You could also talk to the specialist pharmacist Christine Hirsch by telephoning 'mobile telephone number'.

Hospice Headed Notepaper

Centre number:

Patient identification number for this study:

CONSENT FORM

Comparing the treatments currently used in Hospices to treat "throat rattles"

Name of researcher: Christine Hirsch

Please initial box

1. I confirm that I have read and understood the Information sheet dated.....for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected in any way.

3. I understand that sections of any of my or my relatives medical notes may be looked at by responsible individuals from the Hospice or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

I agree on behalf on my relative to take part in the above study.

Name of Patient _____ Date _____ Signature _____

Name of relative or carer and relationship to patient
if signing on behalf of patient.

Date _____ Signature _____

Name of person taking consent _____ Date _____ Signature _____
(if different from researcher)

Researcher _____ Date _____ Signature _____

Appendix C

Data collection form

STUDY OF ANTICHOLINERGICS IN CHEST-RATTLE

Intervention and outcome recording form Page 1

HOSPICE NAME

PATIENT REG NO		Study No.	
Date of entry to study	/ / 00	Time of entry into study	: hrs
How long were symptoms of noisy breathing present before entry into study :			
More than 24 hours	Less than 12 hours	Less than 6 hours	Unknown

1 2
3 4

1. Was yellow or green sputum noted at any time ?	Yes	No	1 2 3 4		
2. a) Has any explanation of cause of chest rattle or drug treatment been given to carers or relatives at any time ?	Yes	No	Don't know	Other	1 2 3 4
b) If 'other' please expand if possible					
3. Consciousness of patient	Conscious	Unconscious	Fluctuating	1 2 3	
4. What words do you feel best describe the chest or throat noises ?					
5. Is patient only patient in single room ?	1	or multi-bedded ward ?	2	1 2	

STUDY OF ANTICHOLINERGICS IN 'CHEST RATTLE'

Intervention and outcome recording form Page 3

Patient study No.

Patient Hospice Reg No.

Have any effects below which may be due to the anticholinergic drug been noted at any time by medical, nursing, paramedical staff or visitors ?

Dry mouth

Thickened secretions

Restlessness/ agitation

Urinary retention

Please describe any other effects experienced by the patient which may be attributable to the anticholinergic drug.

1

2

3

4

Appendix D

Information for ward staff:

Study Summary

Entry into study, monitoring and data collection

Using the noise meter

THE USE OF ANTICHOLINERGIC AGENTS TO TREAT EXCESSIVE OROPHARYNGEAL AND TRACHEAL SECRETIONS IN PALLIATIVE CARE

Study Summary

Medical Staff Involvement in the study

Consent

- After much discussion with groups of medical and nursing staff it was felt most appropriate for consent to be sought by the admitting doctor.
- As the study no change in current treatment consent will be sought from all patients admitted to the hospice unless the admitting doctors feel it inappropriate.
- If admission to the study is considered inappropriate, reasons should be given and recorded in the patients notes.
- Relatives or carers involved in the questionnaire will be consented by CH or another specifically named healthcare professional.
- An information leaflet and consent form has been designed for patients and carers and approved by the Ethics Committee (MREC and LREC). Copies are included at the back of the study folder.
- Signed consent forms will be filed in the study folder and a copy will be put in the patient's records.

Nursing staff involvement in the study

Subjective and objective monitoring of 'rattle noise'.

- **Entry into the study.**

If consent has been obtained, any patient developing noisy breathing or 'rattle' requiring intervention with anticholinergic drugs should be entered into the study. If it is felt that a previously consented patient can not be entered into the study, reasons for this should be recorded on a proforma sheet.

1. Subjective monitoring

A proforma has been designed and piloted to allow collection of subjective rating of 'rattle noise' by the attending nursing staff. Subjective scoring allows for an absolute rating of rattle and also a change in rattle following intervention and on a regular basis. Copies of the proforma will be found in the appropriate section in the folder, (pages 1 and 2) together with further details on how to complete the form.

2. Objective monitoring

To introduce objectivity to the study, the methodology includes the use of a hand held noise meter. Written instructions and training will be given to nursing staff in the use of the noise meter. Recording requires the nurse to hold the meter in a horizontal plane towards the patient at a distance of 40cm (Approximating to hand to elbow distance). The meter is used for three breaths and the maximum score recorded on the proforma.

See objective monitoring section for further details.

3. Adverse events and details of patient symptoms

Relevant descriptive details regarding 'rattle' symptoms and any adverse effects experienced attributable to anticholinergic agents should also be recorded. These are recorded on page 3 of the proforma.

If a patient has to be withdrawn from the study, reasons should be recorded on the proforma.

Pharmacist involvement (CH) including data collection

1. Recording of concomitant medication

As other prescribed drugs may have an effect on the requirements for anticholinergic drugs, all patients developing 'rattle' and entered into the study will have their drug charts reviewed by CH. Details of all drugs administered at the same time as anticholinergic agents will be recorded.

2. Patient carer and relative interviews.

CH or other specifically named healthcare professional will conduct these face-to-face interviews with an appropriate carer or relative attending the patient, (in agreement with the doctor or senior ward nurse); at the time that anticholinergic treatment is being administered.

CH will keep in touch with the nursing staff by telephone to monitor patients that have been entered into the study.

A copy of the outline questions for interview is included in the study folder.

If there are any questions at any time regarding the study please contact Christine on (mobile phone no.) . Please leave a message if the call cannot be taken immediately.

The study is expected to continue for at between three and six months at Compton Hospice depending on numbers of patients recruited.

Entry into the study, monitoring and data collection

1. Consent

- Any patients whom the doctors consider may require anticholinergic therapy for excessive secretions may be entered into the study.
- This may be appropriate on admission, but may be done after admission at an appropriate time.
- (It should be emphasised that this study does not change current treatment practice for this symptom. The monitoring of outcome of treatment is however more formalised.)
- Consent forms should be filed in the in the study folder in the appropriate section. CH will file a copy of the consent form in patients medical notes.

2. Entry into the study

- Any member of the trained nursing staff may enter a consented patient into the study. Please check patients medical notes or the appropriate sections in the study folder to ensure that consent forms have been signed.
- Patients will be assigned a study number to protect anonymity in the study analysis.
- A list of study numbers is available in the study folder. The patients name and hospice number should be recorded on the sheet against the next consecutive number. This number will then appear on all study recording sheets for that patient, rather than a name.

3. Monitoring outcome of interventions for noisy breathing

Data recording form page 1

After the patient has been entered into the study please record on page 1 of the recording form:

- The patient study number from the study record sheet
 - Date and time of entry into study
 - How long symptoms had been present (tick box)
 - Whether sputum was noted (tick box)
 - If you are aware that noisy breathing has been discussed with close relatives or carers in attendance (tick box or expand if possible)
 - Whether the patient is conscious
 - How you would describe the noise
 - If patient is in a single room alone or multi-bedded ward
- (The coding boxes down the side of page one do not have to be completed)

Data recording form page 2

This form should be used to record any interventions made to treat noisy breathing and the subjective and objective outcome of the interventions.

1. On entry to the study, and after any intervention for noisy breathing please record:

a) Subjective outcomes of interventions

- Baseline NOISE SORE (0-3 as per key)
- Time
- Date
- Signature
- Intervention (I =stat injection, T= turning, P= position change, D = syringe driver, S= suction)

b) Objective outcome of intervention

Maximum noise meter measurement over three breaths as detailed in section "Noise meter measurements"

Record as a number in against sound meter reading.

2. At 30 minutes and 1 hour after the intervention. Please repeat measurements a) and b) above **and** record any subjective change in noise level in the top part of the record chart.

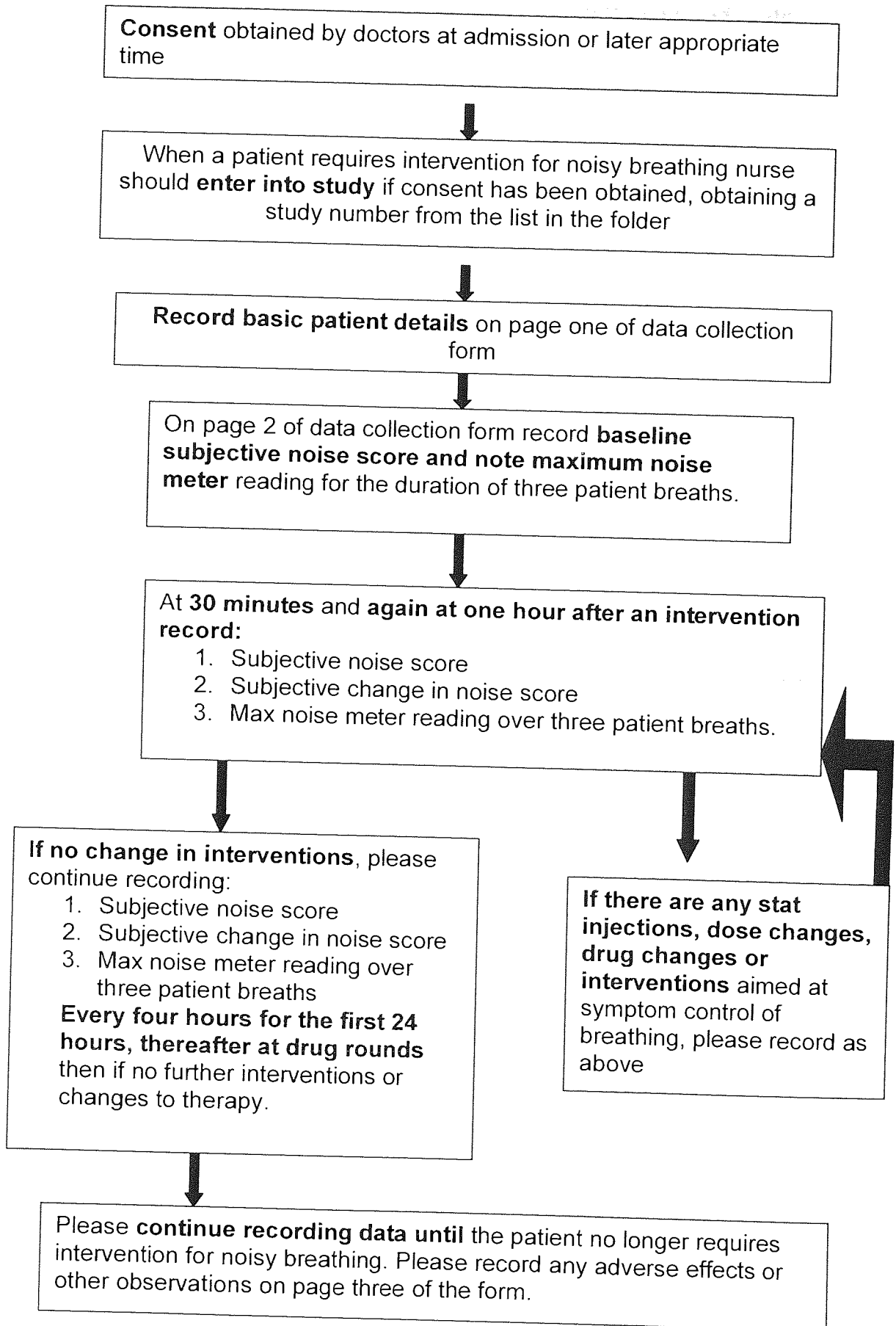
3. Please repeat measurements every four hours for the first 24 hours, then at drug round times after that. If other interventions are made, including stat injections, please record as above.

Data recording form page 3

Please record any adverse effects which you feel may be due to the anticholinergic drug.

Please record time and date that outcome monitoring is stopped and reason for stopping.

Summary flow-diagram of in-patient study process

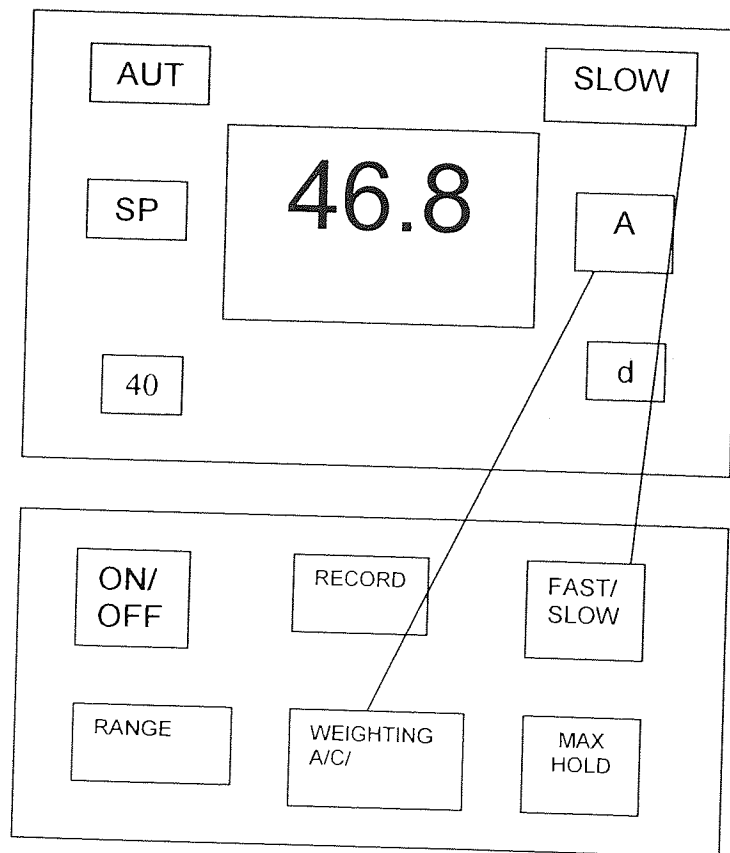


Using the Noise Meter

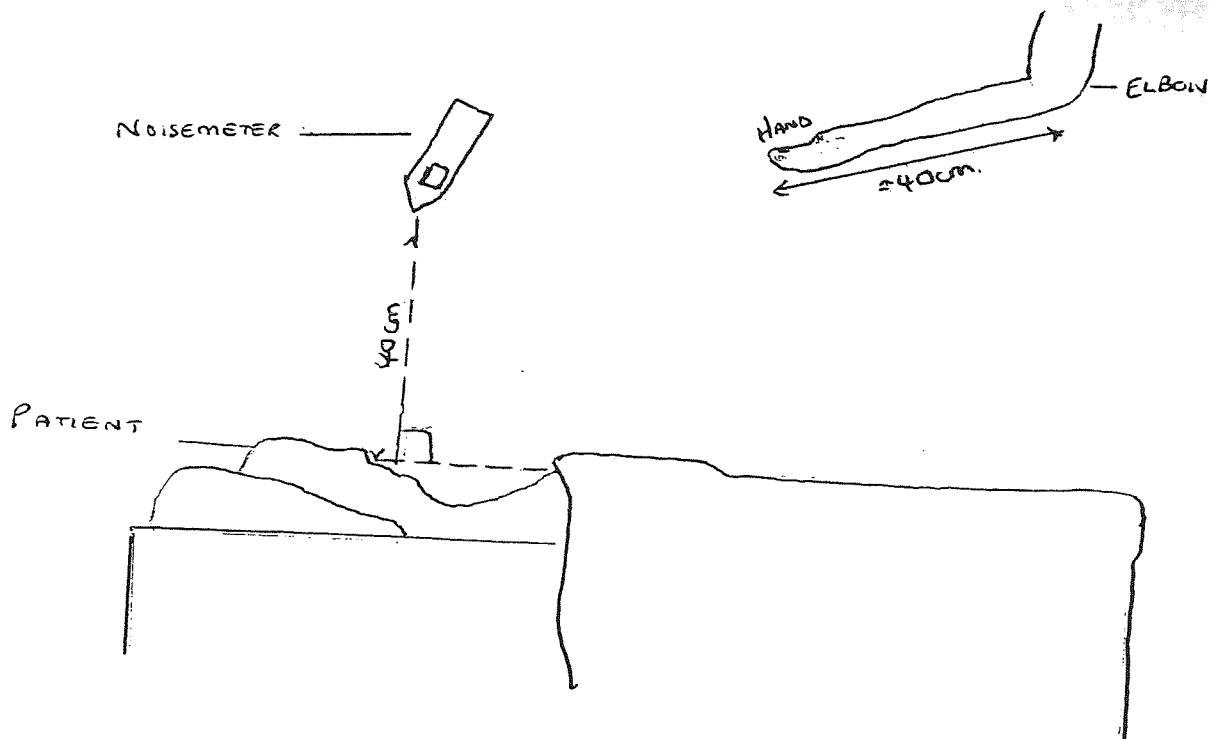
Objective method of sound measurement by sound meter

Please don't be put off by the display on the sound meter

1. Switch the sound meter on by **pressing the orange 'on/off' button**. The unit will display a full screen and then settle down.
2. By pressing the **'fast/slow' button make sure that 'SLOW'** appears on the right hand side of the screen.
3. Under 'slow' on the screen should be an **'A'**. If this is not so please press the **'weighting A/C'** button once which should change a 'C' to 'A'.
4. Top left of the screen should **read AUTO**. If not switch the machine off and back on again.
5. Bottom left of the screen **should read 40**



6. Hold the noise meter 40cm away from the patient at 90 degrees to an imaginary line between the patient's nose and their xiphisternum (bottom of breast bone). This distance is approximately equal to the distance from your elbow to fingertips.



7. Hold the 'pointed' end of the meter towards the patients face, in a plane that is directly in front of the patients face. Tilt the noise meter screen 45 degrees from the patients face so that you can read the meter.
8. Watch the meter whilst the patient takes three consecutive breaths, noting the maximum reading for each breath. Record the reading which is the middle highest of the three readings.
9. If there is a large variation in the readings, repeat the reading which was different. Background noise will register on the meter. Please note if there is unusual noise in the vicinity.
10. Record the noise meter reading on the appropriate box on page 2 of the chart.
11. Turn off the noise meter.

If you have any problems with the noise meter please contact Christine on 07976 589390.

Appendix E

Relative or Carer structured interview questions

Relative or carer consent form

Carer Questionnaire

Comparing the treatments currently used in Hospices to treat 'throat rattles'

Questions to be used in one to one structured interview between researcher and carer or relative.

1. Do you feel that **the patient** is, or has been distressed by noisy breathing or 'throat rattles' ?

No - A little - A lot - Difficult to know

2. Do you feel that **you** are, or have been distressed by noisy breathing or 'throat rattles' from the patient ?

No - A little - A lot - Difficult to know

3. Could **you** say whether you feel that noisy breathing from the patient has a large or small effect on your over-all feelings of distress or emotion at this time?

No effect – small effect – some effect – large effect – very large effect

Other

4. If you feel able to comment, to what extent do you feel that noisy breathing or 'throat rattles' may contribute to overall distress **the patient** is feeling at this point in time?

No distress – some distress – much distress – difficult to know

5. Do you feel that treatment to try and reduce the noisy breathing has helped:

a) The patient at this time ? Yes – No – Difficult to know

b) You at this time ? Yes – No – Difficult to know

6. Are there any other words which you would like to use, or points which you would like to make about noisy breathing or the treatment of noisy breathing ?

.....

.....

.....

Thank you for agreeing to answer these questions at this time.

Christine Hirsch Research Pharmacist.

October 2000 v2

Centre number:

Patient identification number for this study:

CONSENT FORM TO COMPLETE CARER QUESTIONNAIRE

Comparing the treatments currently used in Hospices to treat 'throat rattles'

Name of researcher: Christine Hirsch

Please initial box

1. I confirm that I have read and understood the Information sheet dated for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my or my relatives medical care or legal rights being affected in any way.
3. I agree to take part by answering the questions on the study questionnaire.

Name of relative or carer _____ Date _____ Signature _____

Name of patient

Name of person taking consent _____ Date _____ Signature _____
(if different from researcher)

Researcher _____ Date _____ Signature _____

Appendix F

Invitation letter to attend focus groups

Focus group consent form

Hospice headed notepaper

Anticholinergics for noisy breathing in palliative care. Information sheet for Focus Group Participants

Dear

You have been invited to take part in a focus group as part of a study looking at the use of anticholinergic drugs, in palliative care. Before you decide to take part, it is important that you understand what will be involved.

A brief background to the study

Anticholinergic drugs such as hyoscine hydrobromide, hyoscine butylbromide (Buscopan) or glycopyrronium are routinely used to treat patients with noisy breathing in the terminal stages of their illness in palliative care. This study is using different methods to investigate the use and efficacy of these drugs in the palliative care setting. The focus group has been chosen as a study method, to gain an insight into the experiences and feelings about the administration of these drugs by specialist health care professionals.

The Focus Group

You have been asked to join a group consisting from the ward at Hospice. You are invited to take part in a discussion about the symptomatic treatment of noisy breathing in palliative care. I shall facilitate the session which will last approximately 1 hour. Refreshments will be made available.

The focus group will be held on At.....

The discussion will be audiotaped and later transcribed. You will be asked to identify yourself briefly at the beginning of the session to aid in transcribing of the tape. No further reference will be made which might allow identification of any individuals in any further report or publication which may result from this study.

Confidentiality will be observed at all times. Likewise you must accept an obligation not to disclose or discuss any issues raised after the session has closed.

If you decide to take part you will be asked to sign a consent form. Should you wish to withdraw from the group at any time you may do so.

The study will form part of my PhD thesis based at Aston University. If you need any



Aston University

Content has been removed for copyright reasons

Centre No.

Group No.

CONSENT FORM

Title of Project. **The use of anticholinergic drugs in the treatment of noisy breathing in palliative care.**

Name of researcher: Christine Hirsch

1. I confirm that I have read and understood the information sheet version 2 for the Focus Group for the above study and have had the opportunity to ask questions.

2. I understand that the Focus Group will involve group discussion about the use of anticholinergic agents in the treatment of noisy breathing and that the session will last about one hour.

3. I agree to the session being audio-taped for the purpose of transcription but that no further reference will identify individuals in any further report or publication arising from this work.

4. I understand that all information shared in this discussion should be treated confidentially in terms of individual input and should not be discussed further outside this group.

5. I agree to take part in this focus group.

.....
Name of participant

.....
Date

.....
Signature

.....
Name of researcher
Focus group consent from Vs 2.

.....
Date

.....
Signature

Appendix G

Results (Section 7.2)

Mean noise levels in decibels (dB) with increasing distances from the recorded death rattle sound (Axes 1 to 7)

Table 1. Mean noise level (dB) with increasing distance from noise source (Axis 1)

Distance from source	NOISE LEVEL (dB)					mean
	reading 1	reading 2	reading 3	reading 4	reading 5	
10cm	69.7	79.6	73.2	79.1	79.9	76.3
20cm	69.3	76.6	69.4	66.1	78.8	72.04
30cm	77	77.4	66.2	65	65.2	70.16
40cm	61.6	61.7	62.7	61.9	61.8	61.94
50cm	60.8	60.1	62.4	56.6	59.9	59.96
60cm	58.5	58.3	58.6	56.4	57.8	57.92
70cm	58.6	55.3	58.1	53.6	57	56.52
80cm	53.8	55.5	55.6	54	52.5	54.28
90cm	55.1	53.8	54.7	54.3	52.1	54
100cm	54.9	52.1	54.3	52.4	52.5	53.24

Figure 1. Mean noise level (dB) with increasing distance from noise source (Axis 1)

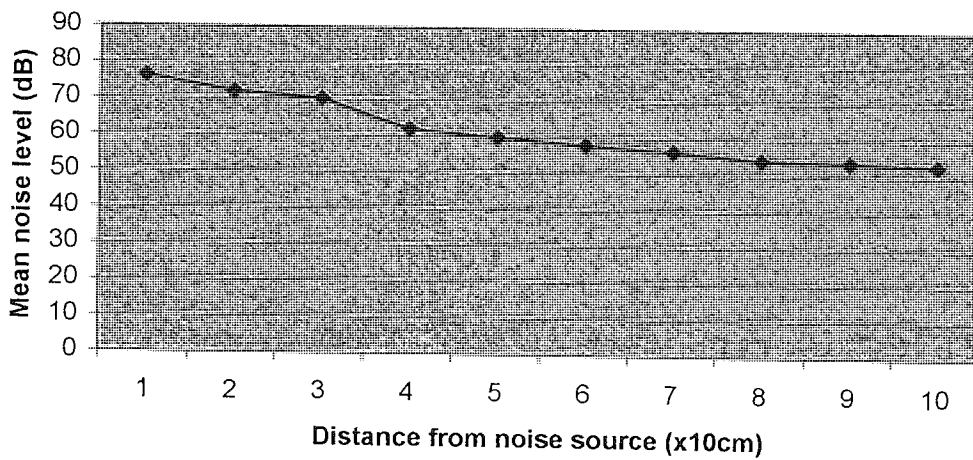


Table 2. Mean noise level (dB) with increasing distance from noise source (Axis 2)

Distance from source	NOISE LEVEL (dB)					mean
	reading 1	reading 2	reading 3	reading 4	reading 5	
10cm	66	78.9	65.2	67.4	66.2	68.74
20cm	64.2	64.8	65.2	64.8	63.7	64.54
30cm	62	61	63.6	62	61.9	62.1
40cm	59.1	58.2	60.6	59.1	58.7	59.14
50cm	57.5	55.3	57.5	56.5	57	56.76
60cm	54.8	53.8	54.7	54.5	56.3	54.82
70cm	53.9	53.2	55.1	53.4	54.9	54.1
80cm	53.4	52.6	55.3	53.2	53.4	53.58
90cm	51.8	52.8	52.3	52.6	53.4	52.58
100cm	50.3	50	55.1	53.4	50.5	51.86

Figure 2. Mean noise level (dB) with increasing distance from noise source (Axis 2)

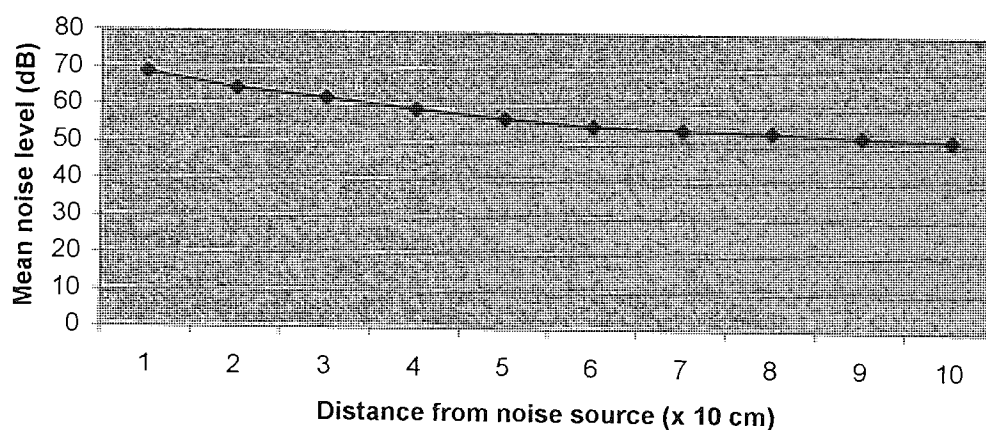


Table 3. Mean noise level (dB) with increasing distance from noise source (Axis 3)

Distance from source	NOISE LEVEL (dB)					mean
	reading 1	reading 2	reading 3	reading 4	reading 5	
10cm	66.7	79.6	79.8	68.6	68.5	72.64
20cm	64.6	64.1	63.7	61.2	60.9	62.9
30cm	59.9	60.3	60.7	59.7	59.1	59.94
40cm	58.5	59.3	59.2	57.4	57.3	58.34
50cm	56.9	57.5	57.3	58.4	56.3	57.28
60cm	56.2	55.6	56.3	56.2	55.4	55.94
70cm	54.8	54.2	55.6	55.7	54.8	55.02
80cm	55.2	52.5	53.3	52.8	52.1	53.18
90cm	55.3	53.9	52.6	52.2	52.4	53.28
100cm	53.6	54.4	52.9	51.9	52.5	53.06

Figure 3. Mean noise level (dB) with increasing distance from noise source (Axis 3)

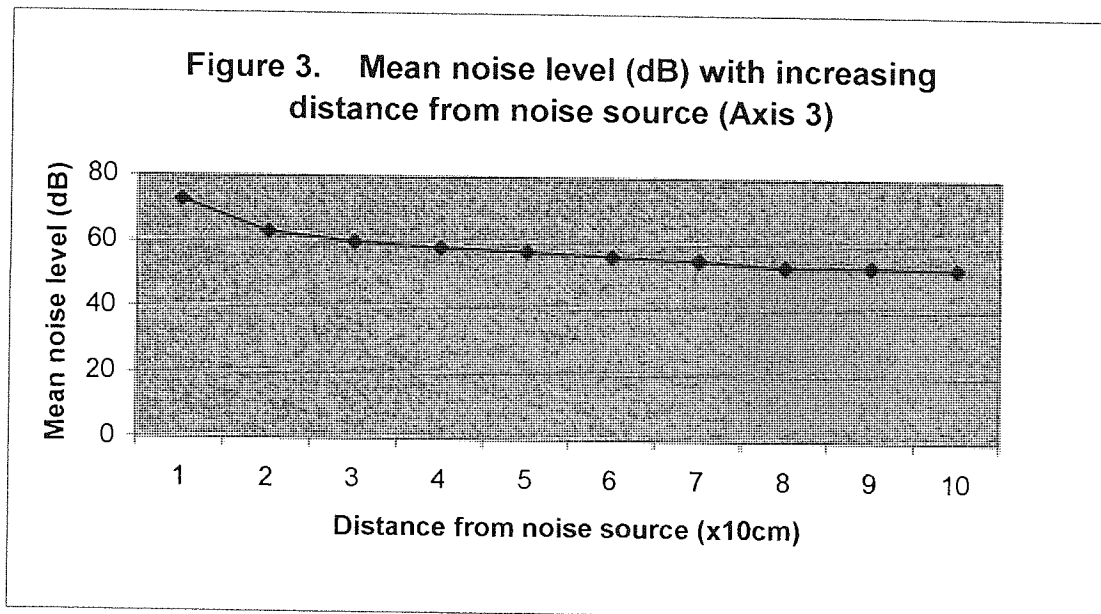


Table 4. Mean noise level (dB) with increasing distance from noise source (Axis 4)

Distance from source	NOISE LEVEL (dB)					mean
	reading 1	reading 2	reading 3	reading 4	reading 5	
10cm	70.8	78.6	78.2	65.6	60.9	70.82
20cm	63.9	63.4	61	60.9	63	62.44
30cm	59.8	59.9	56.3	58.4	57.9	58.46
40cm	57.7	57.3	54	55.1	55.6	55.94
50cm	54.6	54.7	52.6	53.3	54.2	53.88
60cm	54.3	54.3	50.4	50.5	53.2	52.54
70cm	52.3	52.4	49.1	52.1	49.7	51.12
80cm	51.4	50.3	49.6	49.4	51.2	50.38
90cm	51.3	50.9	48.6	49	50.6	50.08
100cm	51.6	50.1	48	48.3	47.9	49.18

Figure 4. Mean noise level (dB) with increasing distance from noise source (Axis 4)

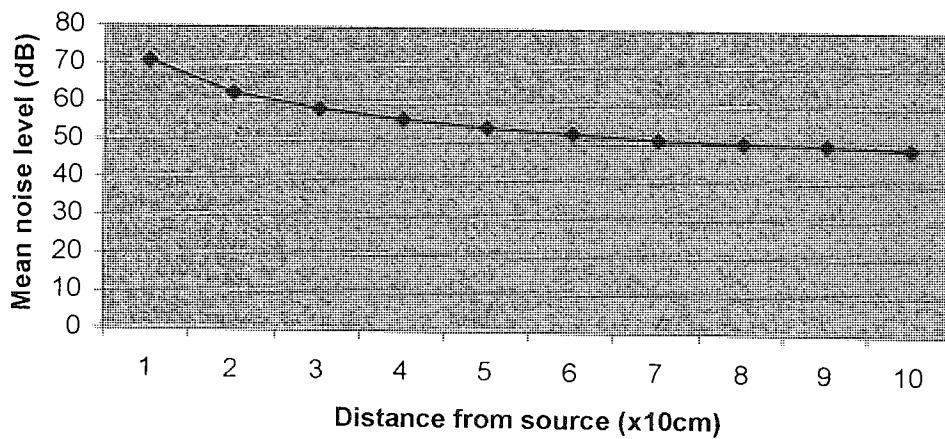


Table 5. Mean noise level (dB) with increasing distance from noise source (Axis 5)

Distance from source	NOISE LEVEL (dB)					mean
	reading 1	reading 2	reading 3	reading 4	reading 5	
10cm	70.7	70.4	69.3	70.2	70.5	70.22
20cm	66.1	68	66.3	63.3	66.8	66.1
30cm	64.4	62.3	63.4	62.3	63.4	63.16
40cm	61.9	61.3	59.9	59.8	60.4	60.66
50cm	58.4	57.3	57.5	57.3	58	57.7
60cm	58.4	58.2	56.8	58.1	56.7	57.64
70cm	54.6	56	54.5	55.7	56.4	55.44
80cm	53.4	55.2	54.2	55.2	55.6	54.72
90cm	54.4	55.9	54	54.3	53	54.32
100cm	53	54.3	53.5	53.7	55	53.9

Figure 5. Mean noise level (dB) with increasing distance from noise source (Axis 5)

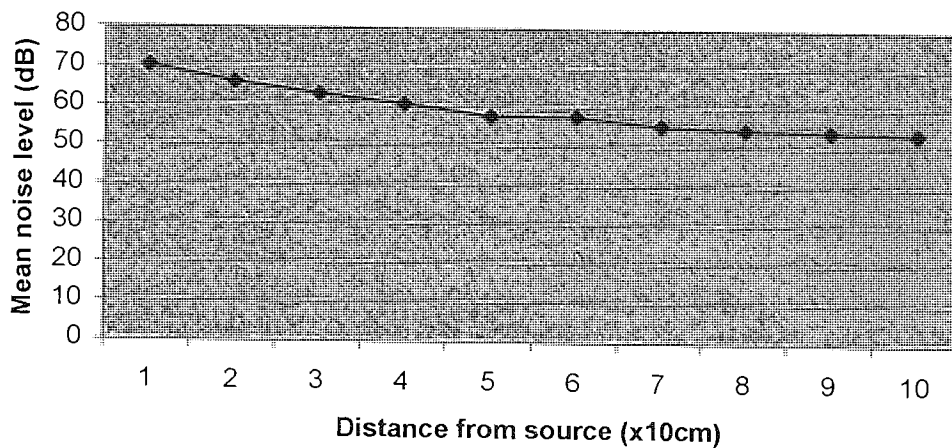


Table 6. Mean noise level (dB) with increasing distance from noise source (Axis 6)

Distance from source	NOISE LEVEL (dB)					mean
	reading 1	reading 2	reading 3	reading 4	reading 5	
10cm	67.9	79.9	68.3	79.4	66.5	72.4
20cm	60.2	60.3	60.8	61.1	61.3	60.74
30cm	56.2	55.9	55.4	56.7	57.3	56.3
40cm	54.2	55.1	55.4	57.3	53.4	55.08
50cm	52.4	52.8	53.4	52.6	51.6	52.56
60cm	54.4	51.9	52.6	52.7	52.5	52.82
70cm	50.9	51.1	51.8	52.1	51.6	51.5
80cm	51.2	50.5	50.5	51.5	49.9	50.72
90cm	51.2	52	51.9	51.4	50.1	51.32
100cm	48.9	49.7	49.6	50.1	50.5	49.76

Figure 6. Mean noise level (dB) with increasing distance from noise source (Axis 6)

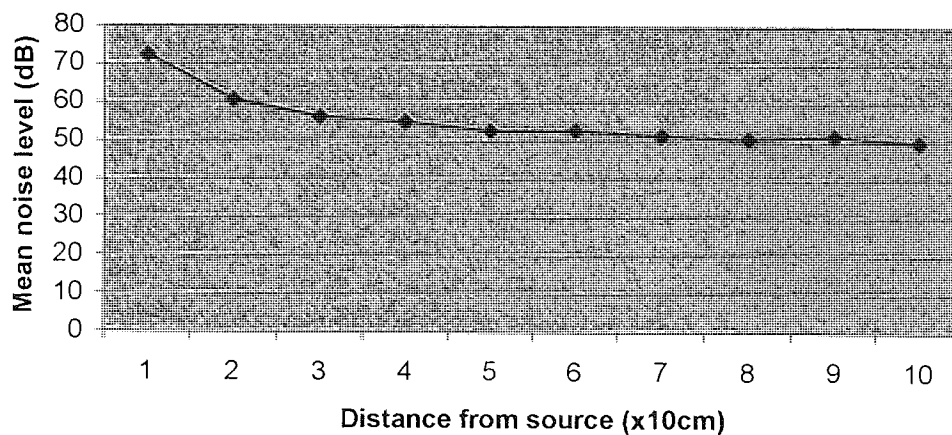
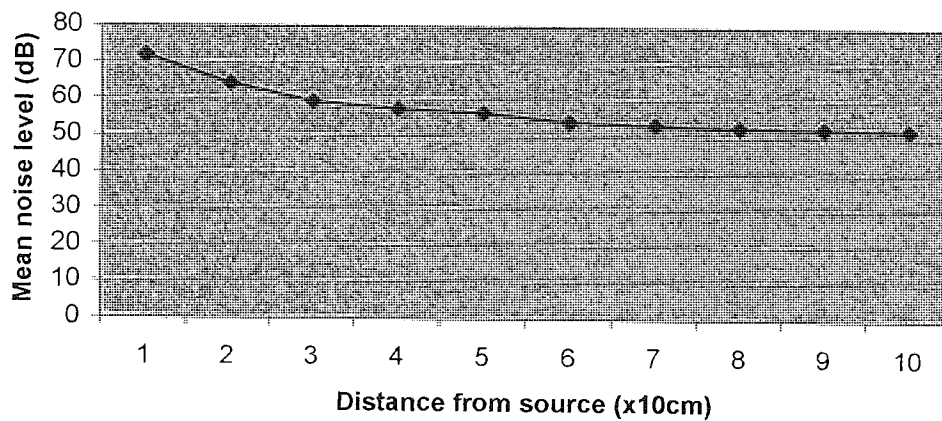


Table 7. Mean noise level (dB) with increasing distance from noise source (Axis 7)

Distance from source	NOISE LEVEL (dB)					mean
	reading 1	reading 2	reading 3	reading 4	reading 5	
10cm	74.8	71.3	71.2	71.1	71.2	71.92
20cm	64.6	63.3	62.9	64.4	65.8	64.2
30cm	60.4	60.1	58.7	58.4	59.1	59.34
40cm	59.3	56.3	57.6	56.9	57	57.42
50cm	56.3	55.8	56.2	56.7	56.8	56.36
60cm	55.6	54.1	53.8	53.2	53.4	54.02
70cm	55.6	53	52	52.5	53	53.22
80cm	53.8	52.4	52.4	52.6	52.2	52.68
90cm	52.9	51.9	52	52.8	53	52.52
100cm	52.1	52.4	52.9	52.1	51.4	52.18

Figure 7. Mean noise level (dB) with increasing distance from noise source (Axis 7)



Appendix H

Focus group thematic coding spine

Focus Group Thematic Coding Spine

Category	Sub-category 1	Sub-category 2	Sub-category 3
Drugs used to treat death rattle	Anticholinergics	Hyoscine hydrobromide	Bolus Injection Infusion Transdermal
		Hyoscine butylbromide	Bolus Injection Infusion
		Glycopyrronium	Bolus injection Infusion
	Effectiveness, anticholinergics		
	Anticholinergics, Side effects		
Concomitant medication			
Non drug intervention for death rattle	Positioning		
	Suctioning		
	Explanation and reassurance		
Death rattle symptoms	Noisy breathing		
	Secretions		
	Distress	Distress, family Distress, patient Distress, staff Distress, Others	
Culture, Hospice	Pre-emptive prescribing		
	First line drug treatment		
	Healthcare professional hierarchy, preconceptions		
Culture, community	De-luxe dying		
	Empowerment of family/carers		
	Pressure from family/carers		
	Drug availability		
Knowledge, healthcare professionals	Drugs		
	Pathology		
	Evidence		
Prescribing/ administration decisions			

Appendix I

Patient case profiles

Appendix I

Patient Case Profiles for Hospice 1 and Hospice 2

Each patient case profile consists of

- A table showing the results of the noise recording data collated for each patient including data from noise meter readings where this was available, together with the subjective noise scoring plus relevant data extracted from the patients medical records.
- Where the data was available, a graphical representation of the interventions received by each patient for death rattle and the corresponding noise levels with time, shown for each patient.

The case profiles are in profile number order (Numbers prefixed with C first, followed by those prefixed with SM), in three groups depending on the characteristics of the data that was recorded.

Group 1 – Noise meter data, subjective noise scoring and background data from the patients' medical records was available.

Group 2 – Subjective noise scoring data and background data from the patients' medical records was available

Group 3 – Background data from the patients' medical records only was available

The key below applies to all of Appendix I.

Key:

HHBr = hyoscine hydrobromide

HBBr = hyoscine butylbromide

GLY = glycopyrronium

'None noted' – nothing noted in the patients medical records of relevance to the observations in the present study, or nothing noted on the study data collection sheet.

For the graphs:

Red font = bolus subcutaneous injections

Green font = continuous subcutaneous infusions via a syringe driver

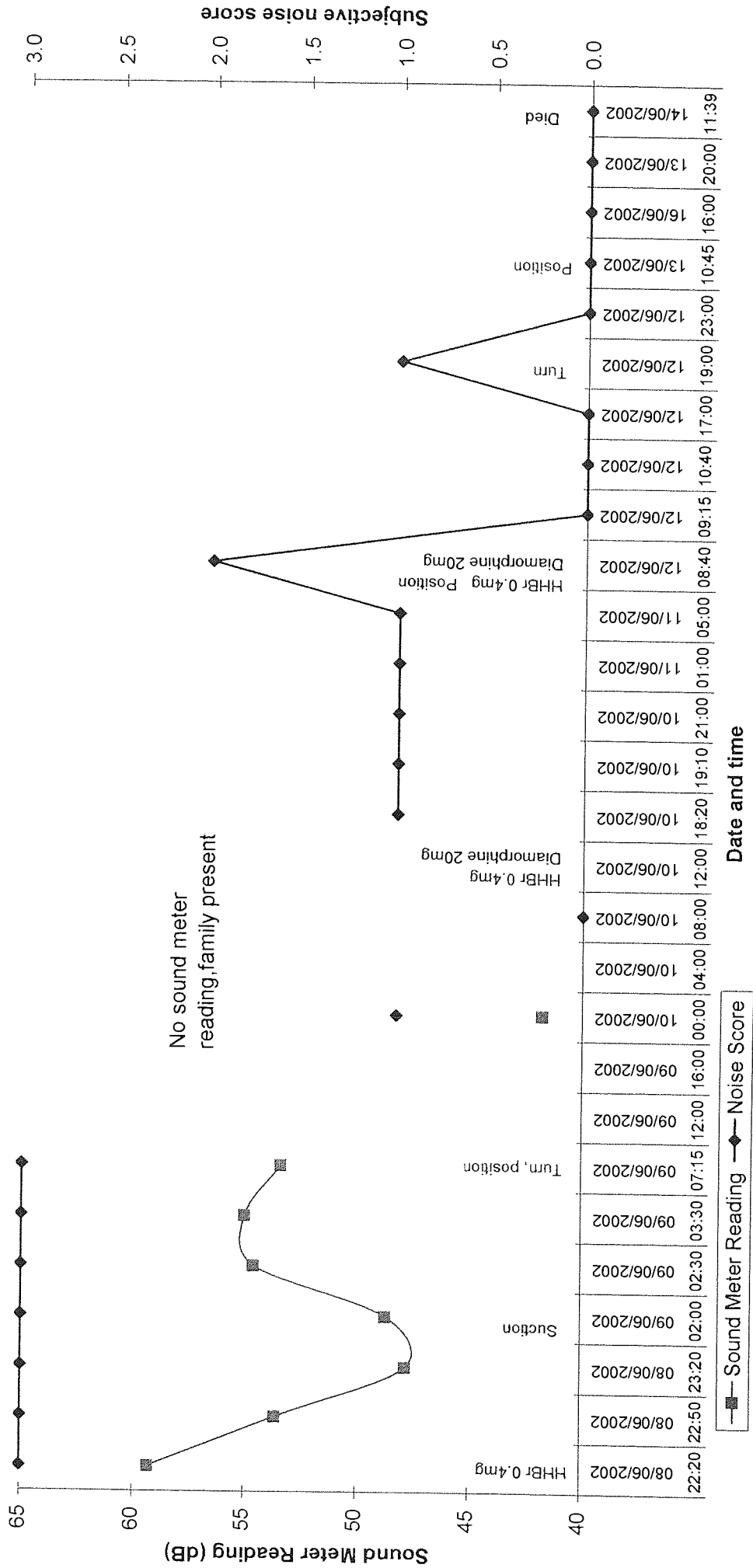
Black font = other medication

Brown font = other interventions for death rattle

Group 1 –Patient case profiles where noise meter data, subjective noise scoring data and background data from the patient’s medical records was available.

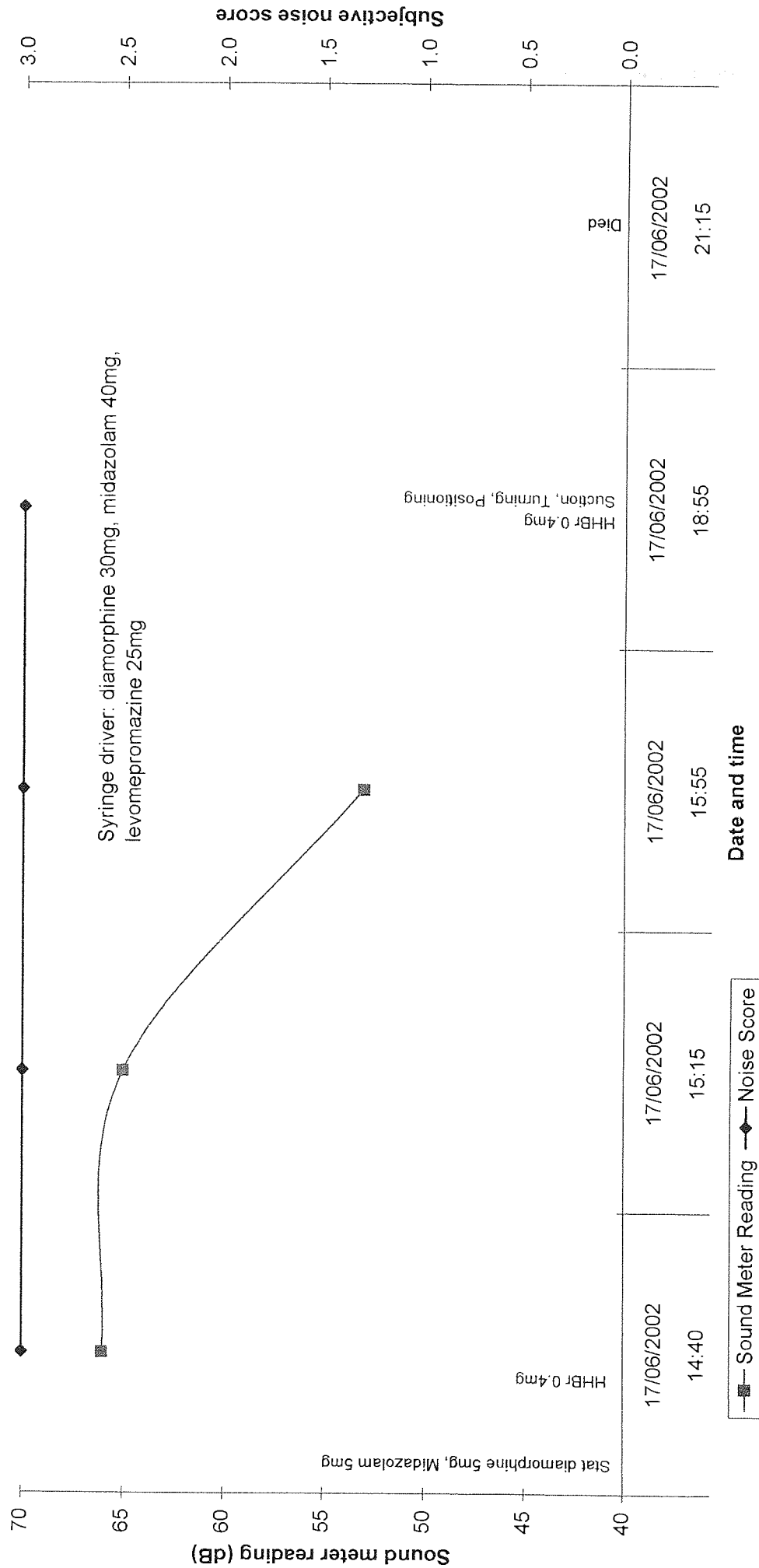
Case Profile C004	A 72 year-old female patient with squamous cell carcinoma of the oesophagus.
Relevant Past Medical History	Ischaemic heart disease, angina and hypertension with a previous myocardial infarction. Levobulonol eye drops prescribed for glaucoma. Spironolactone prescribed prior to admission (discontinued 11 days prior to entry into the study). Medical notes indicated that the patient had developed bronchopneumonia, for which previous antibiotic treatment had been prescribed.
Study entry /consent issues	None noted
Concomitant medication	Two stat dose diamorphine 2.5mg with HHBr
Treatment for noisy breathing	The patient received three stat injections of HHBr 0.4mg, the period between the first two being 44 hours and 38 hours between the second and third. The noise meter data indicated a decreased noise level after the first bolus hyoscine injection (although subjectively no change was recorded, remaining maximal at 3). Half an hour after the HHBr injection the noise meter reading dropped from 59.3dB to 53.6dB and one hour later to 47.8dB. After the second bolus injection of HHBr no change in the subjective score was recorded, however 38 hours later a peak in the subjective score resulted in a further bolus injection of HHBr 0.4mg. Thirty five minutes after the injection subjective score was 0. However patient’s position was altered at the same time. Diamorphine injection was also administered simultaneously. Further peaks of noisy breathing appeared to have responded to turning
Noise monitoring notes	The noise meter was used at the start of the treatment but then stopped (reportedly due to deterioration of the patient and family presence). The deterioration did not correspond with any increase in noise levels. Subjective noise score at this point was 1. Turning and position were also recorded on the chart at this time This level of monitoring was carried out for nine hours, apart from one further reading when the family was absent, a noise meter reading of 41.8 corresponding to a subjective score of 1. Although subjective scoring was continued, albeit less frequently until the patient’s death over the following six days, subjectively noise levels were noted in the patient’s medical records as ‘minimal’ and ‘a lot better’. At a subjective noise score of ‘1’ patient was recorded in the notes as having a ‘quiet night’ and ‘no hyoscine needed’.
Adverse effects	None noted
Other comments	None noted

Case profile C004



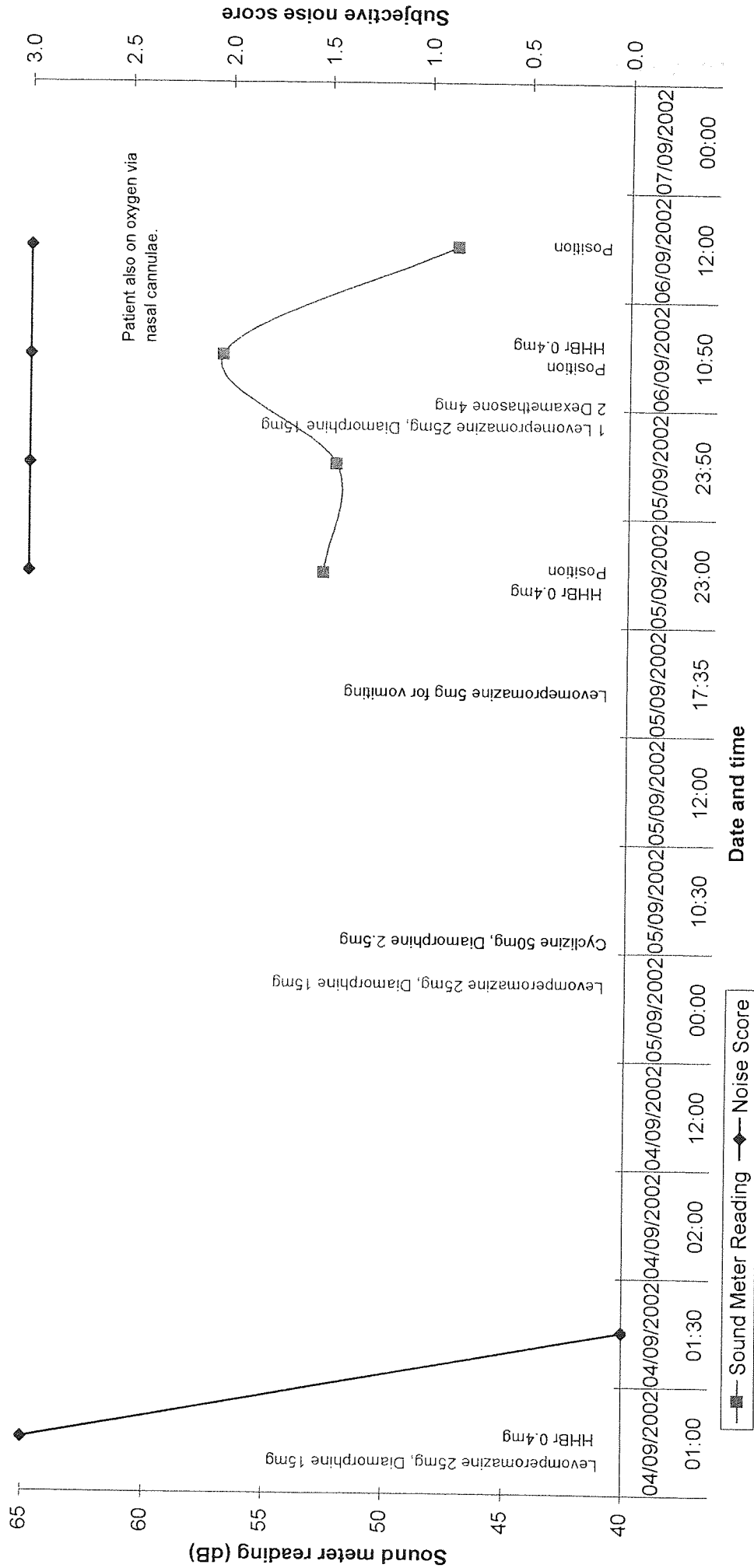
Case Profile C005	A 46 year-old female with a glioma
Relevant Past Medical History	Admitted for symptom control. Episodes of being 'unroutable', headaches and hallucinations noted in the medical records. Admitted on the 11 th June and on 17 th became very chesty with upper respiratory tract secretions documented in the medical records.
Study entry /consent issues	Patient was in a single room, with all family present at the time of consent. Family had refused treatment for the rattle for some time. But then they found they could not stay in the room with the noise. A carer questionnaire was conducted with the patient's sister
Concomitant medication	A syringe driver was started containing diamorphine, midazolam and levomepromazine for analgesia, as an antiepileptic and sedation for agitation
Treatment for noisy breathing	A bolus HHBr 0.4mg injection was given when the secretions were noted. A second bolus HHBr 0.4mg injection was administered after 4 hours and 15minutes. At the same time as suction and turning was carried out.
Noise monitoring notes	There was no response to a bolus injection of HHBr on the subjective noise score. Although the noise meter readings decreased after 35minutes and after 75 minutes from baseline, no change noted at all with the subjective score which remained at 3. The subjective noise score remained at 3. No further noise meter readings were taken but a further bolus HHBr 0.4mg injection with turning. The response to this intervention was not recorded and the patient died 1 hour and 20 minutes later. Three noise meter scores of 66dB, 65dB and 53dB corresponded to subjective noise scores of 3, classed as the same, or worse. A further subjective score of 3, four hours after the injection resulted in suction being applied together with a further injection of HHBr.
Adverse effects	Comment during one of the focus group sessions made reference to this patient reflecting that the secretions had become overwhelming after the second injection of HHBr.
Other comments	None noted.

Case profile C005



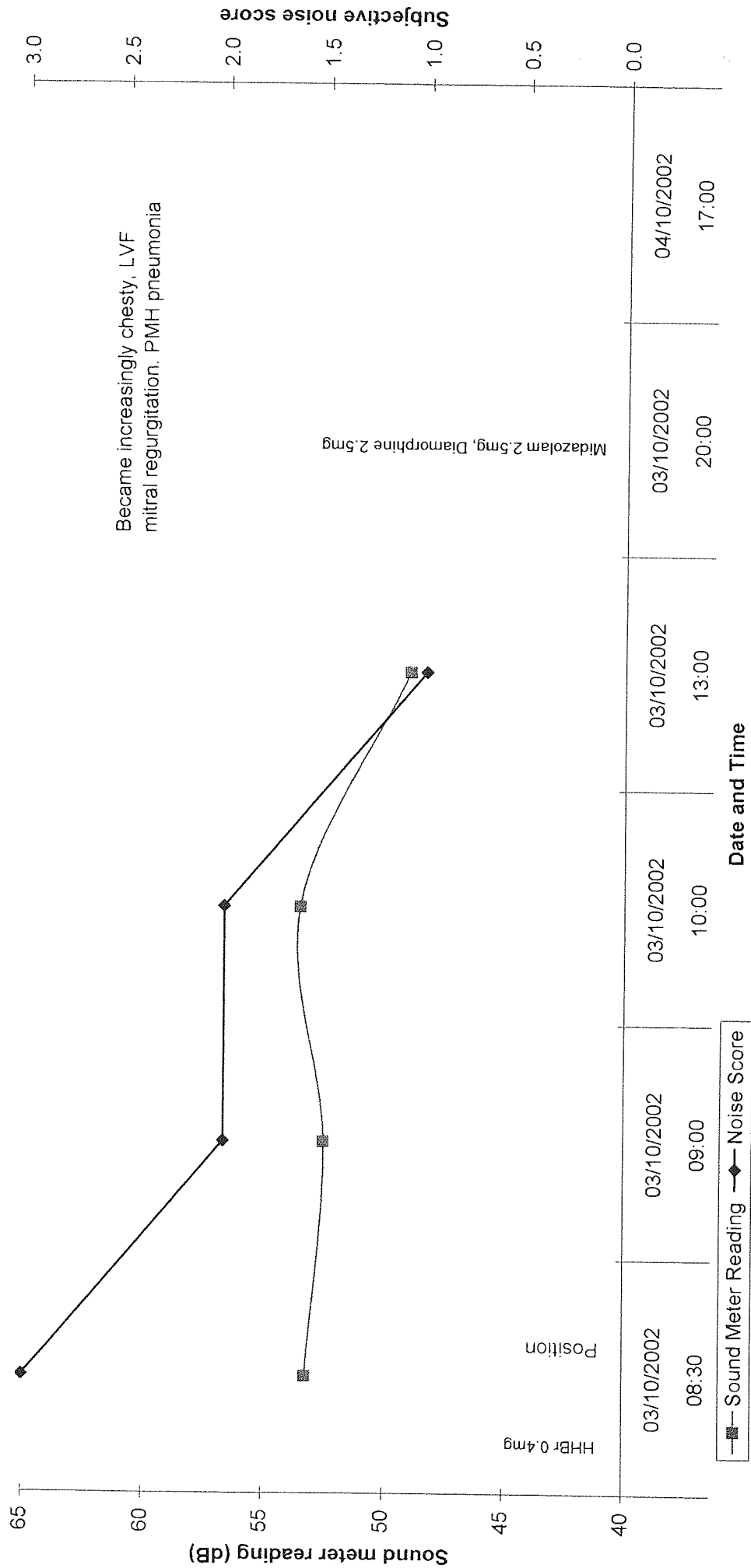
Case Profile C006	A 76 year-old female with an unknown primary carcinoma with multiple liver metastases
Relevant Past Medical History	None noted
Study entry /consent issues	The patient was entered into the study at 01:00 on 4/9/02 when the first injection of HHBr was given. An injection of HHBr had been given to the patient on 26/8/02 this was given as a 'one off' when the patient appeared 'chesty'. Nurses reported 'no effect' from this injection and no further doses were given until 4/9/02.
Concomitant medication	The patient had previously been prescribed pilocarpine drops and saliva substitute, but had not received many doses Both had been stopped 4 days prior to entry into the study. This patient was also receiving oxygen via nasal cannulae and was receiving diamorphine and levomepromazine via a syringe driver plus dexamethasone via a second syringe driver. Bolus doses of cyclizine and diamorphine were also given. The patient required medication as shown for vomiting during the study period.
Treatment for noisy breathing	The nursing notes claimed that the first bolus injection of HHBr 0.4mg was given 'with effect'. In all, three bolus injections of HHBr were given, the second 45.5 hours after the first and the third 11 hours, 50 minutes after the second.
Noise monitoring notes	Subjective noise scores dropped from 0 to 3, 30 minutes after the first bolus injection of HHBr. Nursing notes recorded the patient 'settled and appearing comfortable'. The chest then was noted to be 'bubbly again' and a further injection was given. The noise meter was used after the second injection of HHBr and re-positioning was administered. Subjective noise scores remained high in spite of the hyoscine injections. The noise meter recorded a drop in noise level 50 minutes after an injection of HHBr 0.4mg and repositioning. Almost 12 hours later the noise level rose again. A bolus dose of HHBr 0.4mg and re-positioning resulting in a reduction in noise level after 70 minutes – subjective scoring remaining at high at 3.
Adverse effects	None noted
Other comments	Patient was noted to mouth breath and waking expressing thirst and drinking quickly.

Case profile C006



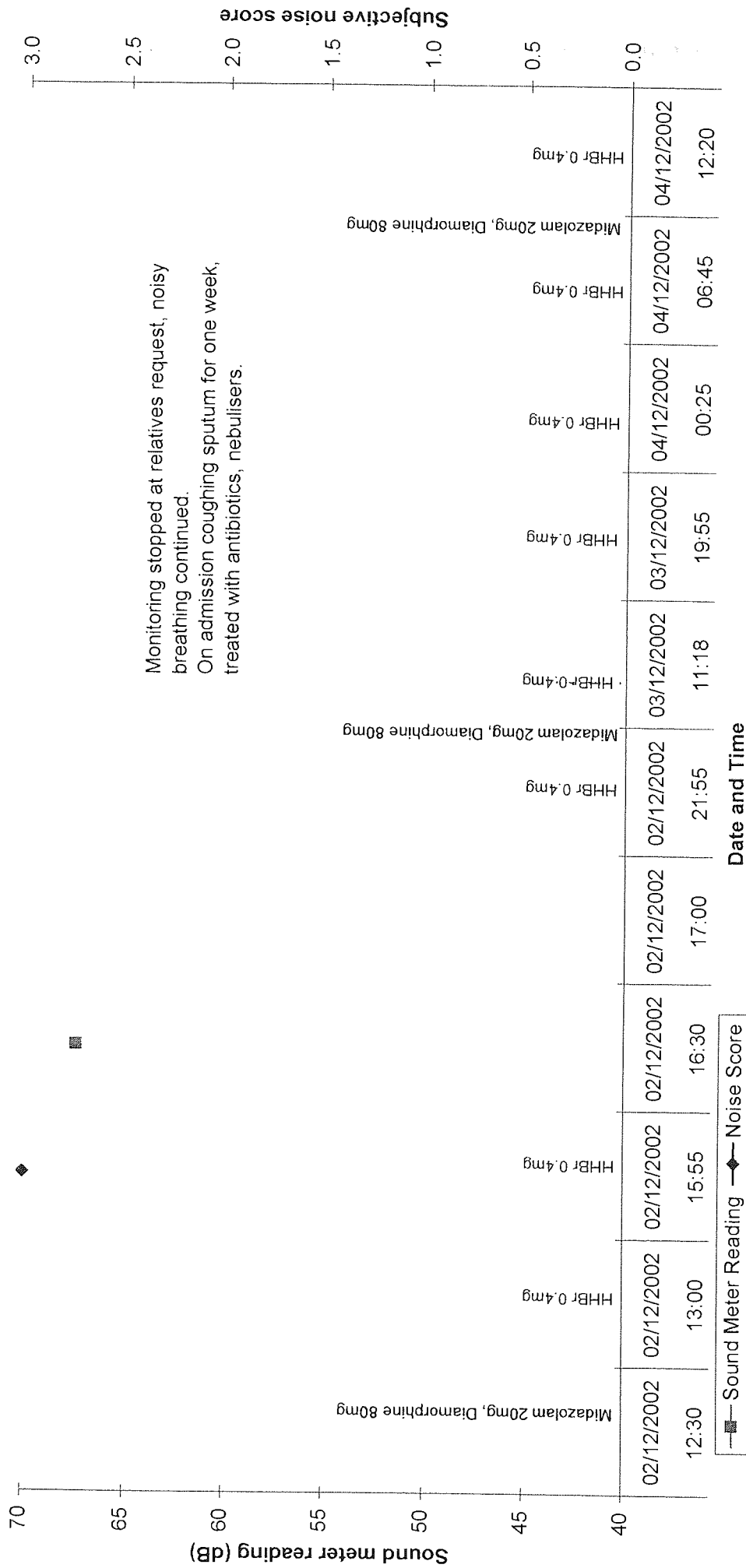
Case Profile C009	A 76 year-old male with carcinoma of the kidney and lung metastases
Relevant Past Medical History	Atrial fibrillation, left ventricular failure, mitral valve regurgitation and a subsequent degree of renal failure.
Study entry /consent issues	Patient was admitted on 17/9/02 and entered into the study on 3/10/02.
Concomitant medication	The patient had previously been prescribed digoxin, tamsulosin, megestrol and warfarin which were stopped on 25 and 26/9/02. The patient had also received a course of amoxicillin followed by clarithromycin, stopped on 27/9/02. A bolus injection of midazolam and diamorphine were administered after monitoring had stopped.
Treatment for noisy breathing	One bolus injection of HHBr 0.4mg was given and the patient's position was changed
Noise monitoring notes	30 minutes after the HHBr injection the change in the noise meter reading was not significant, however the subjective score had reduced from 3 to 2. Although no further medication was administered or other treatment recorded, both noise meter reading and subjective score remained the same for the next hour. Four and a half hours after the initial injection both noise scores were reduced again, noise meter reading by 4.9 dB and the subjective score to 1.
Adverse effects	None noted
Other comments	The patient had received one dose of HHBr however the subjective noise score decreased from 3 to 2 to 1. The noise meter score throughout the study period was above 50dBA. No particular response was noted with the treatment and the patient died on evening of 4/10/02 still 'sounding chesty' recorded at 20:30 hours.

Case profile C009



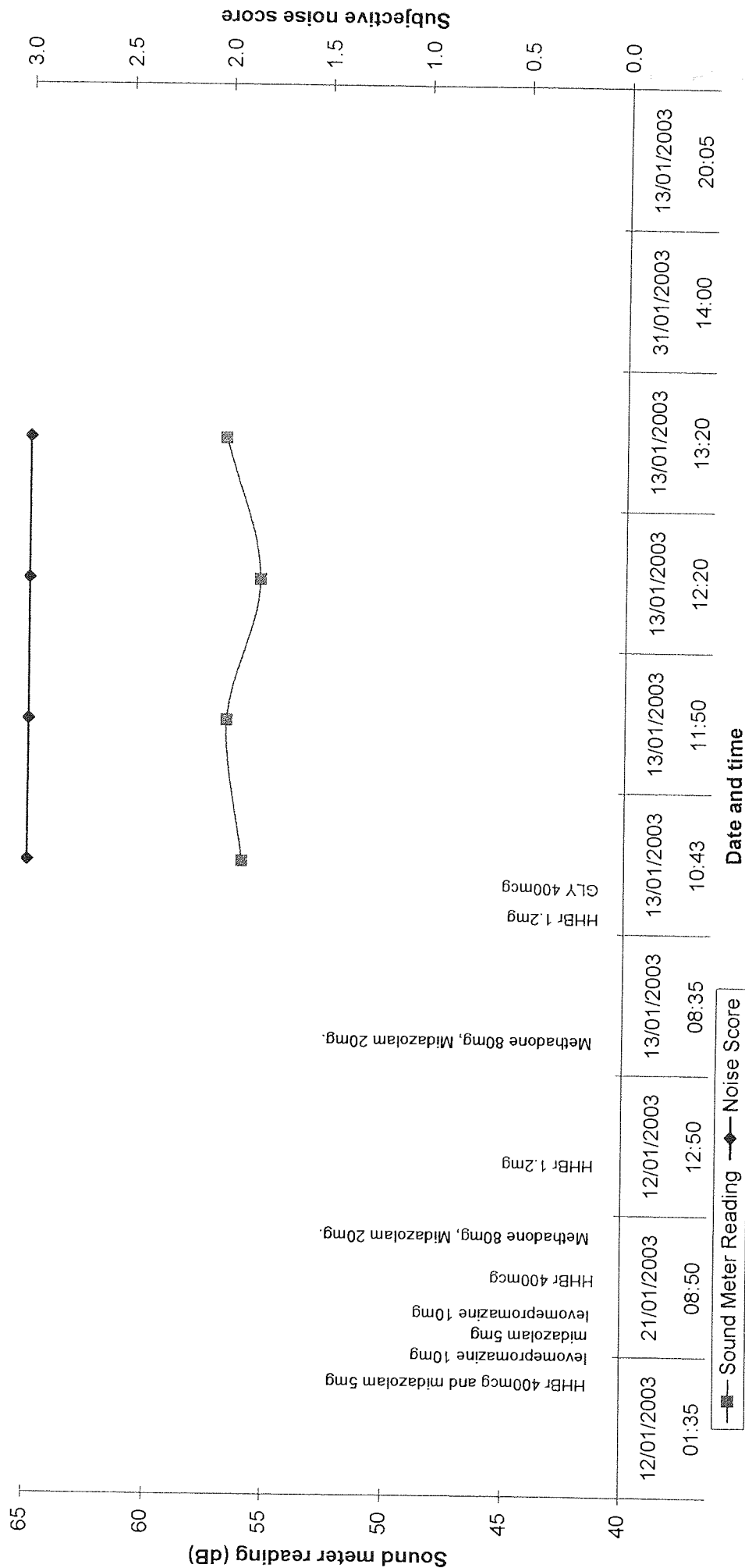
Case Profile C010	A 59 year-old female patient with metastatic non small cell lung cancer
Relevant Past Medical History	On admission (11/11/02) the patient was noted to be coughing with productive sputum, and was given a course of antibiotics
Study entry /consent issues	None noted
Concomitant medication	The patient was also concurrently receiving diamorphine and midazolam via a syringe driver. Oxygen was also being administered via nasal cannulae to this patient. On 1/12/02 Combivent nebules (salbutamol and ipratropium) had been administered for breathing but not during the study monitoring period.
Treatment for noisy breathing	Bolus injections of HHBr were given at the following intervals over the last 76 hours of the patient's life: Bolus HHBr 0.4mg 2hr 55min " 5hr " 13hr 15min " 9 hr 35min " 4hr 25min " 6 hr 15min " 6 hr 30min
Noise monitoring notes	Only one noise meter reading was recorded and one subjective noise score. Noise monitoring was discontinued at the request of the family. It was therefore not possible to compare subjective and noise meter scores, however both the subjective noise score and meter reading were high at 3 and 67.4dB respectively, 2 hours after one bolus HHBr injection and 1.5 hours after a second bolus injection.
Adverse effects	None recorded
Other comments	The patient continued to have noisy respirations throughout the dying phase in spite of repeated injections of HHBr given at different frequencies. Respirations were noted to be noisy but the patient was reported to be comfortable throughout. It was also noted that the patient remained 'poorly and breathless'. 'Some benefit' from the hyoscine injections were noted. Mucus was noted to be coming from the nose earlier on 1/12/02.

Case profile C010



Case Profile C011	A 62 year-old male, primary diagnosis carcinoma of the bronchus
Relevant Past Medical History	The patient was noted to need antibiotics for purulent sputum prior to entry into the study. The patient's medical records over the past month noted symptoms of coughing, for which methadone linctus, and a course of antibiotics (amoxicillin) had been prescribed.
Study entry /consent issues	The patient had received two bolus doses of HHBr prior to consent and a syringe driver administering HHBr for just over 24 hours at entry to the study. Staff would not ask for consent before the weekend as they felt the family were too anxious.
Concomitant medication	The patient was also receiving midazolam plus methadone by sc infusion over 24 hours and had been so prior to study entry. Bolus injections of levomepromazine and midazolam were also given.
Treatment for noisy breathing	Twelve hours before entry into the study, upper respiratory tract secretions were noted to be much greater and a syringe driver of HHBr 1.2mg over 24 hours was started. The syringe driver was renewed the next day at the same dose. In addition a bolus injection of GLY was given just after the syringe driver was started. Nursing staff noted that secretions in the throat caused the patient 'panic'.
Noise monitoring notes	The subjective noise score remained at a maximum at 3. The recorded noise meter level was consistently over 55dB. No change was recorded at any time in the subjective noise score in response to the bolus injection of GLY, and although started before monitoring took place it would appear that there was little or no improvement (none recorded in the medical records) in response to HHBr administration via the syringe driver.
Adverse effects	Although it was noted in the medical records that the patient had not passed urine for over 24 hours, no adverse effects were recorded on the data collection sheet.
Other comments	It was documented that the family were happy that the patient was comfortable.

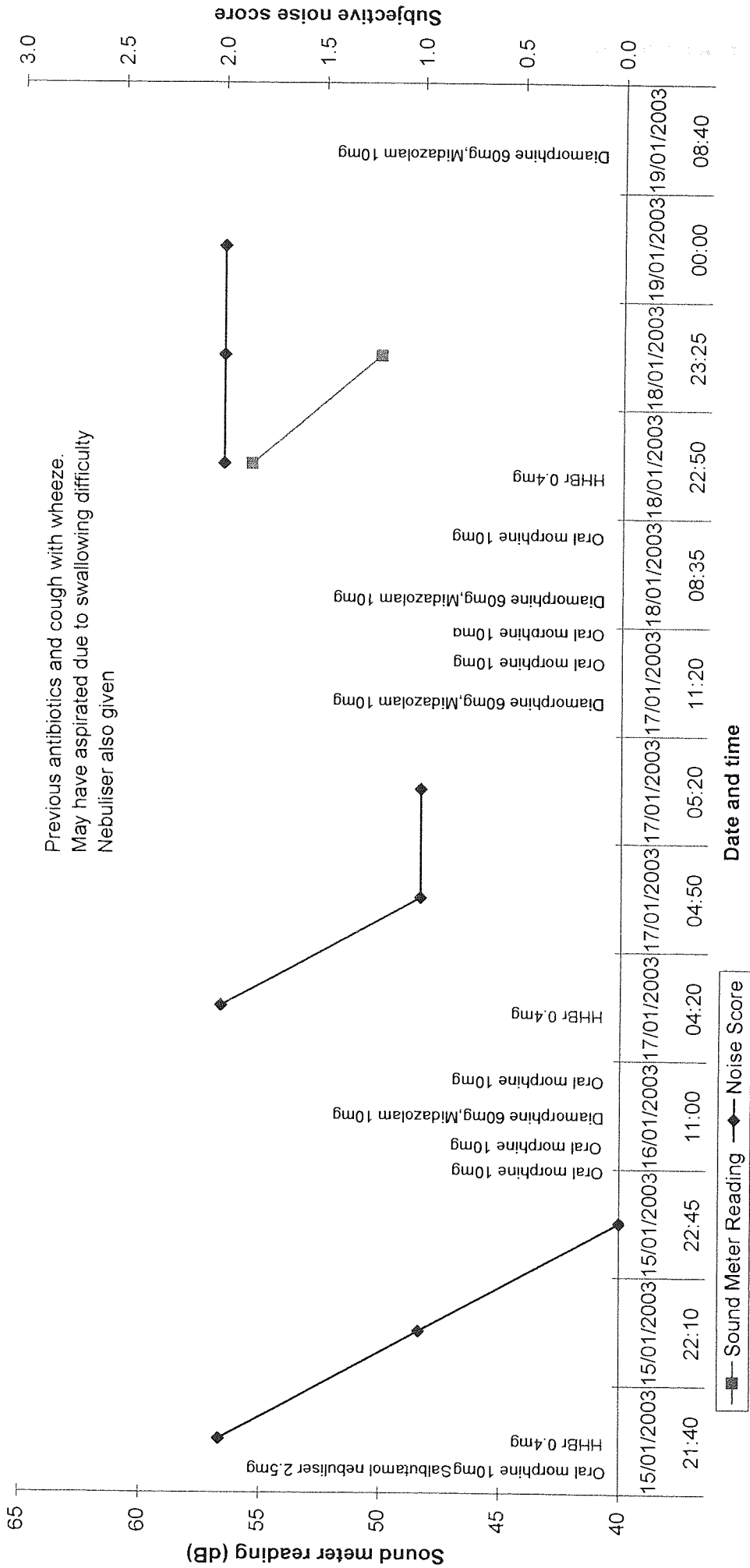
Case profile C011



Case Profile C012	A 65 year-old female with metastatic squamous cell carcinoma of the oesophagus.
Relevant Past Medical History	Coughing, 'multiple crackles throughout' with the possibility of developing pneumonia was noted in the medical records.
Study entry /consent issues	The patient gave consent.
Concomitant medication	Simple linctus had been given for cough and sputum. Admitted on 6/1/03, by 11/1/03 the patient was short of breath, finding it difficult to expectorate sputum. Salbutamol nebules were administered for wheeze. Saline nebules were administered. A syringe driver of diamorphine and midazolam was in place. A course of amoxicillin had been started on 8/1/03.
Treatment for noisy breathing	A bolus injection of HHBr 0.4mg was administered then 28.5 hours later a second injection, and 38 hours later a further injection. Nursing notes in the patient's medical records also reported positioning on 30 degree tilt but this was not recorded on the data collection chart. (17/1/03) was a time when patient was quiet).
Noise monitoring notes	1/2 hour after the first HHBr injection the subjective noise score fell from 2 to one and after an hour to zero. The second injection of HHBr resulted in subjective score improvement from 2 to 1, after 30 minutes but no further improvement. The third injection of HHBr produced no reduction in the subjective score, but a reduction in the noise meter reading of 5.4 dB was noted 35 minutes after the injection.
Adverse effects	None were noted on the data collection chart, but a urinary catheter was inserted 18 hours after the HHBr injection as the patient had not passed urine.
Other comments	Oral morphine was administered but there was no concomitant noise monitoring to see whether this had any effect.

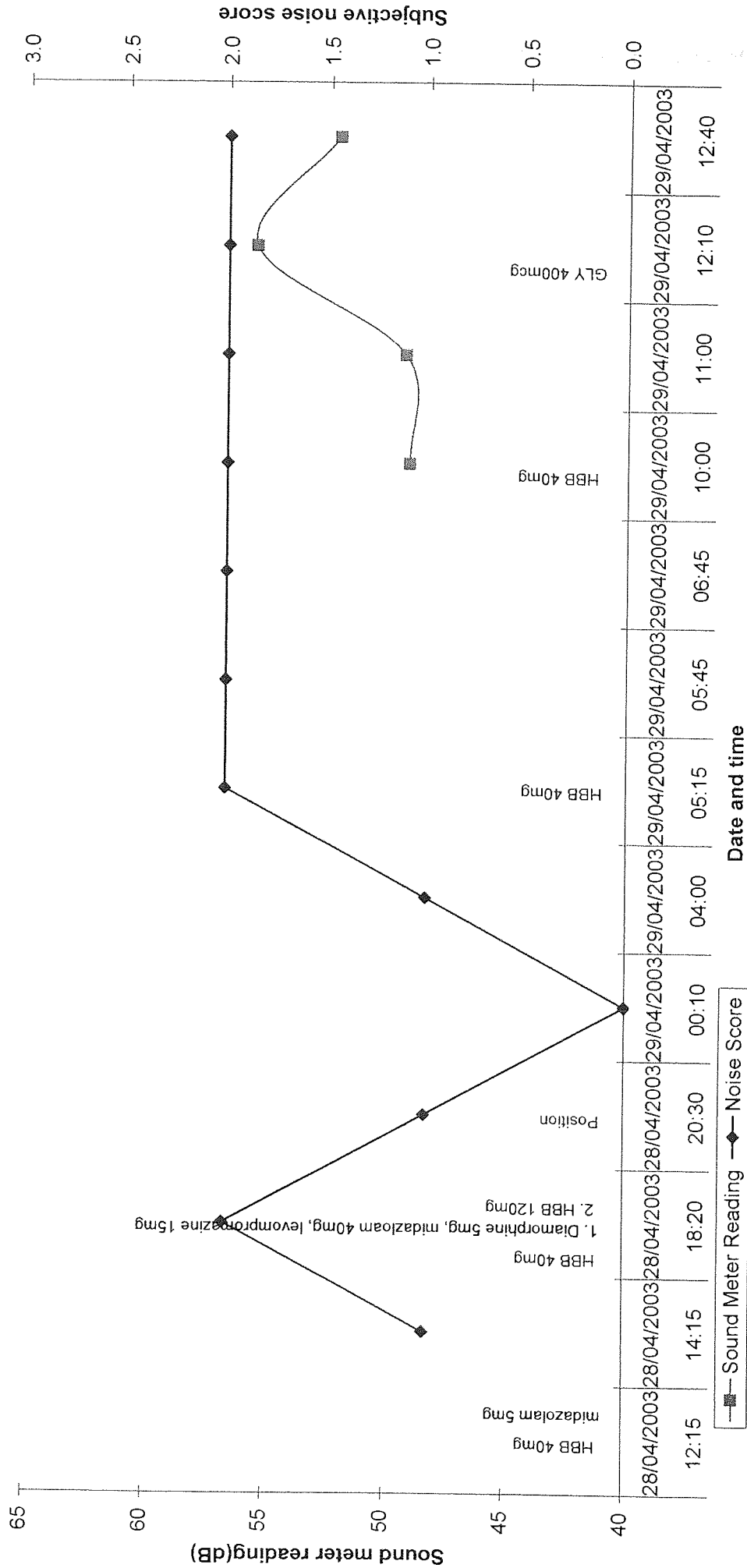
Case profile C012

Previous antibiotics and cough with wheeze.
 May have aspirated due to swallowing difficulty
 Nebuliser also given



Case Profile C013	A 64 year-old male with oesophageal carcinoma and brain metastases
Relevant Past Medical History	The patient also had a history of rheumatic fever.
Study entry /consent issues	Nothing significant noted.
Concomitant medication	Concurrent drugs were levomepromazine, midazolam and diamorphine administered via a syringe driver.
Treatment for noisy breathing	HBBr injection was given 40mg, and later a syringe driver was started with 120mg HBBr. The time period between bolus injections of 40 mg HBBr was 6hrs, 11hrs (with the syringe driver administering HBB 120mg over 24 hours), 5 hours. Two hours later GLY was given
Noise monitoring notes	No baseline reading was taken for the first injection of HBBr 40mg. Six hours later a second bolus injection of HBBr 40mg plus 120mg HBBr in the syringe driver was administered. After two hours the subjective noise score had reduced by 50%, at this point re-positioning was recorded and subjective noise score reduced to 0, a further 50% after 2 1/2 hours. Noise levels increased again to subjective score of 2 five hours later which did not produce a response according to subjective scoring in response to HBBr 40mg or GLY 400mcg. The noise meter was only used to record data at the end of the treatment period. No significant change in the noise meter reading was seen in response to the HBBr 40mg injection at 60 minutes. 30 minutes after the GLY 400mcg bolus was administered the noise meter showed a reduction in noise level of 3.1dB. subjective noise score remained the same. Descriptive rating of the noise level at this time was that it was 'worse' i.e. no response to the treatment.
Adverse effects	None recorded
Other comments	Noted that friend and sister were concerned over bubbly breathing. Overall the picture was one of chest rattle not being relieved by hysocine butylbromide or subjectively by the stat glycopyrronium in this patient.

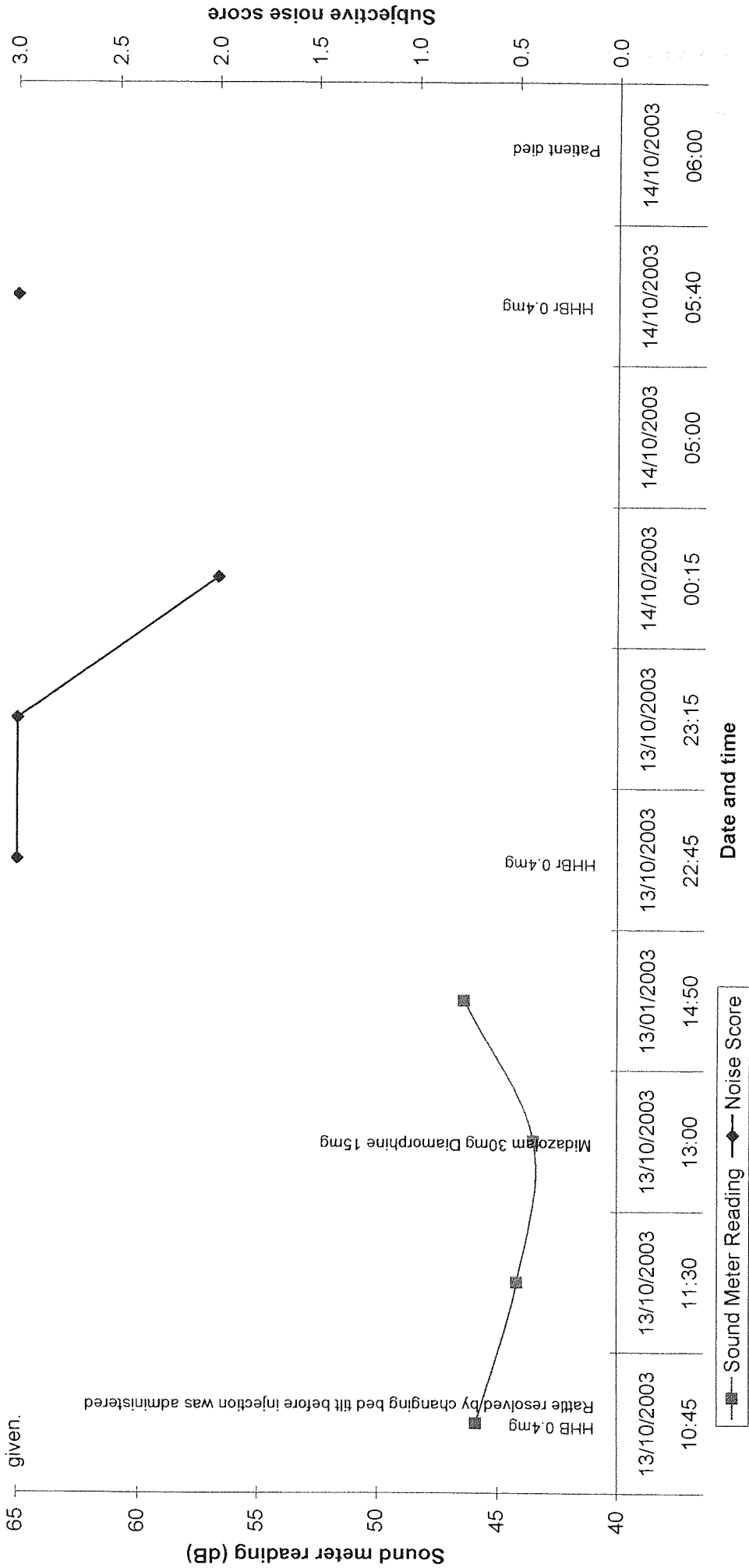
Case profile C013



Case Profile C015	A 69 year-old male with metastatic adenocarcinoma of the lung.
Relevant Past Medical History	Nothing relevant noted
Study entry /consent issues	This patient was consented during a consultant ward round, as the decision to initiate noisy breathing treatment was made. During the consultation, the angle of the patients bed was raised which had the immediate effect of resolving the low level of rattle noise, before the injection of hyoscine was given. Nursing staff felt that the wife was too anxious for interview.
Concomitant medication	The patient was also received diamorphine and midazolam via a syringe driver.
Treatment for noisy breathing	Three bolus injections of HHBr 0.4mg were administered. The interval between the first two injections was noted to be 12 hours, the second 7 hours
Noise monitoring notes	Baseline noise level recording showed no noise (see above) The patient was felt to be too weak to clear his normal chest secretions, although the nursing notes in the medical records claimed 'some relief' from the injection of HHBr on 14/10/03 at 5pm. After the first bolus of HHBr 0.4mg the noise meter showed a reduction of 1.7 dB 45minutes after the first injection. This increased to 2.4 dB overall reduction from initial score after 2 hours and 15minutes. The noise level rose again after 3 hours and 10 minutes. A second injection HHBr 0.4mg at 22:45 hours on 13/10/03 did not result in a change in the subjective noise score after 30 minutes but the subjective noise score had reduced from 3 to 2 after 2.5 hours (no further noise monitoring was done). A further injection of HHBr was required at 05:00 hours however when the subjective noise score had risen to 3.No further monitoring was carried out and the patient died at 6:05 hours. The noise meter may have indicated a response to the first injection although there were no subjective noise scores. Less response however was seen from the later injections.
Adverse effects	None recorded
Other comments	Nurses documented 'some relief' in notes after the second HHBr injection.

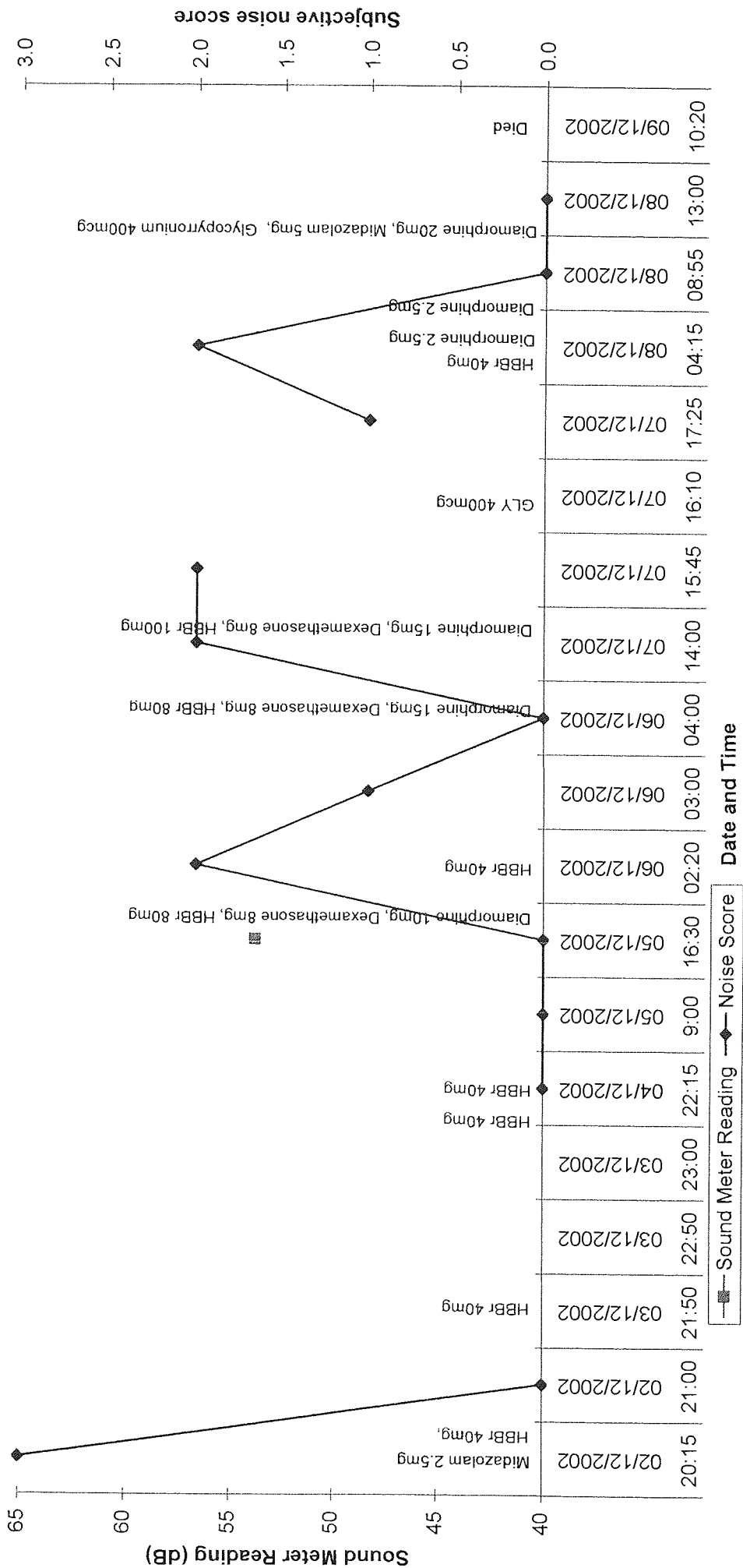
Case profile C015

Raising end of bed at baseline reduced rattle before injection was given.



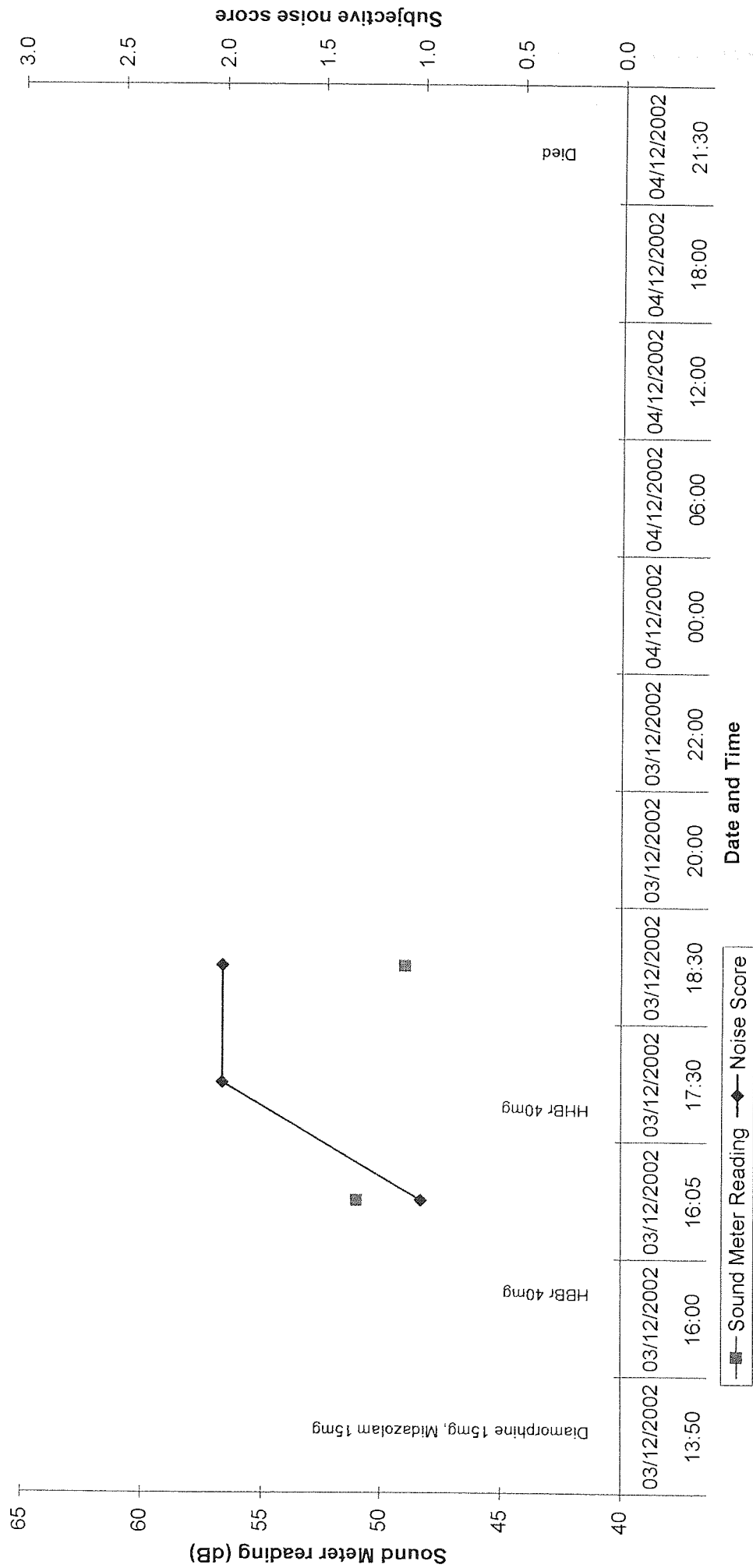
Case Profile . SM102	A 50 year-old male patient with non small cell lung cancer with brain metastases.
Relevant Past Medical History	Patient had previously had pleural effusions which had been drained. Subcutaneous saline infusion was continued until the day before death.
Study entry /consent issues	None
Concomitant medication	A syringe driver containing diamorphine and cyclizine with dexamethasone in a second syringe driver was administered then, dexamethasone with diamorphine together with HBBr was administered via subcutaneous infusion. One bolus subcutaneous dose of midazolam and two bolus doses of diamorphine were given. Ketoprofen was infused subcutaneously via a syringe driver over 24 hours in a separate driver. Sodium chloride was nebulised for coughing with no effect
Treatment for noisy breathing	Bolus injections of HBBr 40mg, together with HBBr 120mg infused via syringe driver over 24 hours. Bolus GLY 400mcg.
Noise monitoring notes	After the first stat HBBr 40mg injection, the subjective noise score fell to 0 after 45 minutes (midazolam was given at the same time). Subjective noise scoring remained at 0. The only noise meter reading recorded was 53.8 dB corresponding with a subjective noise score of 0 . A bolus injection of HBBr was administered when the subjective noise score was 2. The subjective score reduced to 1 after 40 minutes then to 0 after total of 80 minutes. After 10 hours the subjective noise score was again 2 but no further injections were given. Bolus GLY 400mcg was given with a subjective noise score of 2. Seventy five minutes later the subjective noise score was 1. Twelve hours later another bolus injection of HBBr 40mg was given together with diamorphine, (Subjective noise score, 2). Four hours and 35 minutes later the subjective noise score was zero. The nursing notes recorded some good results from the early bolus injections of HBBr. By 8/12/02 bolus HBBr had little effect although the subjective noise score shows a sharp decrease.
Adverse effects	None recorded
Other comments	Wife had been distressed by breathing, a relative interview took place.

Case Profile SM102



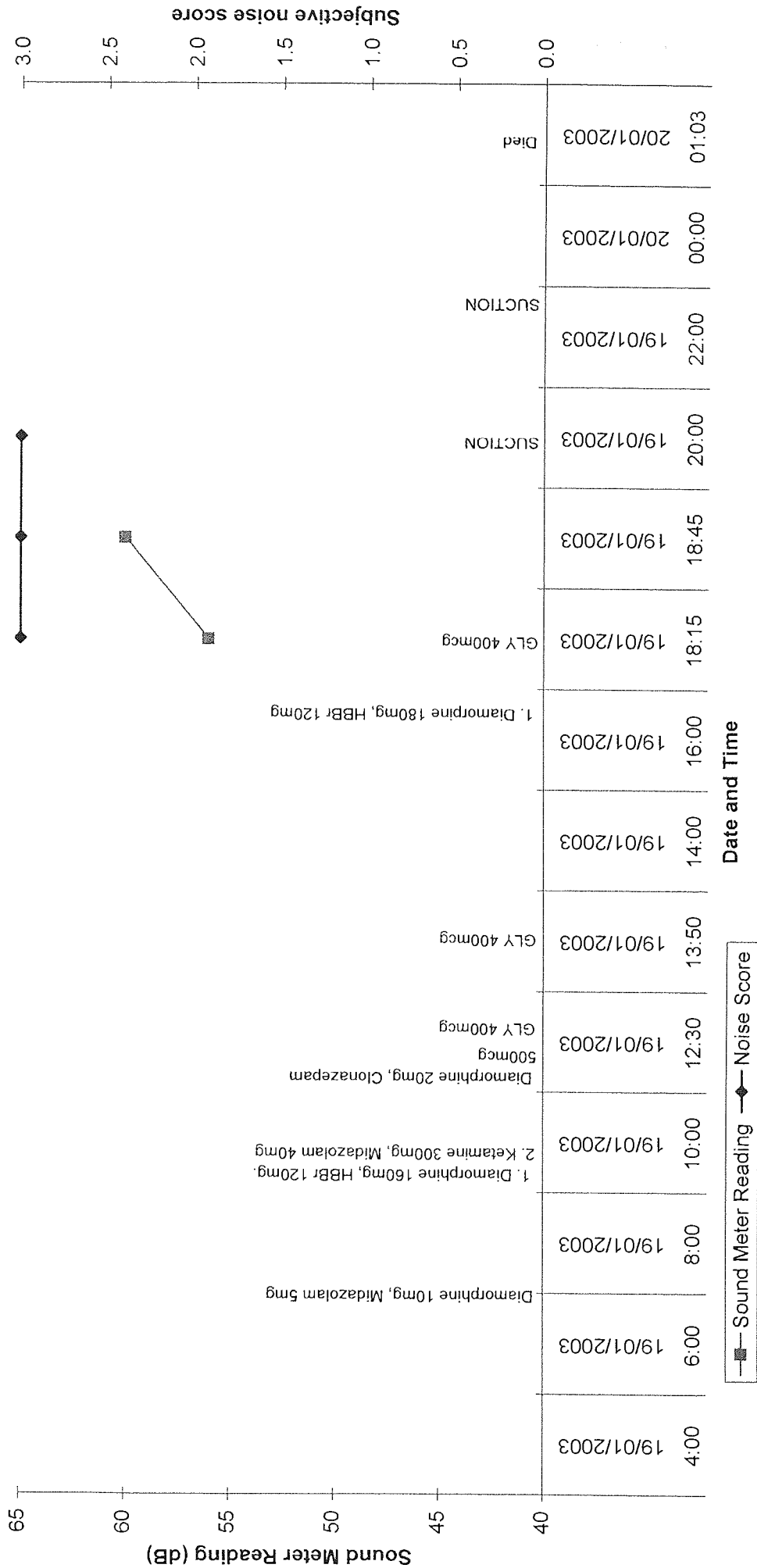
Case Profile . SM103	A 73 year-old female with multiple myeloma
Relevant Past Medical History	None of relevance
Study entry /consent issues	None
Concomitant medication	Diamorphine 15mg and midazolam 15mg over 24 hours via syringe driver.
Treatment for noisy breathing	Two bolus injections HBBr 40mg
Noise monitoring notes	The second noise score was taken 90 minutes after the first blous injection. Subjectively the noise score had increased from 1 to 2 and remained at 2 sixty minutes after the second injection. The noise meter reading decreased by 2 dB.
Adverse effects	None recorded.
Other comments	Breathing was noted to be 'laboured and bubbly'. Subcutaneous saline infusion was continued in this patient

Case Profile SM103



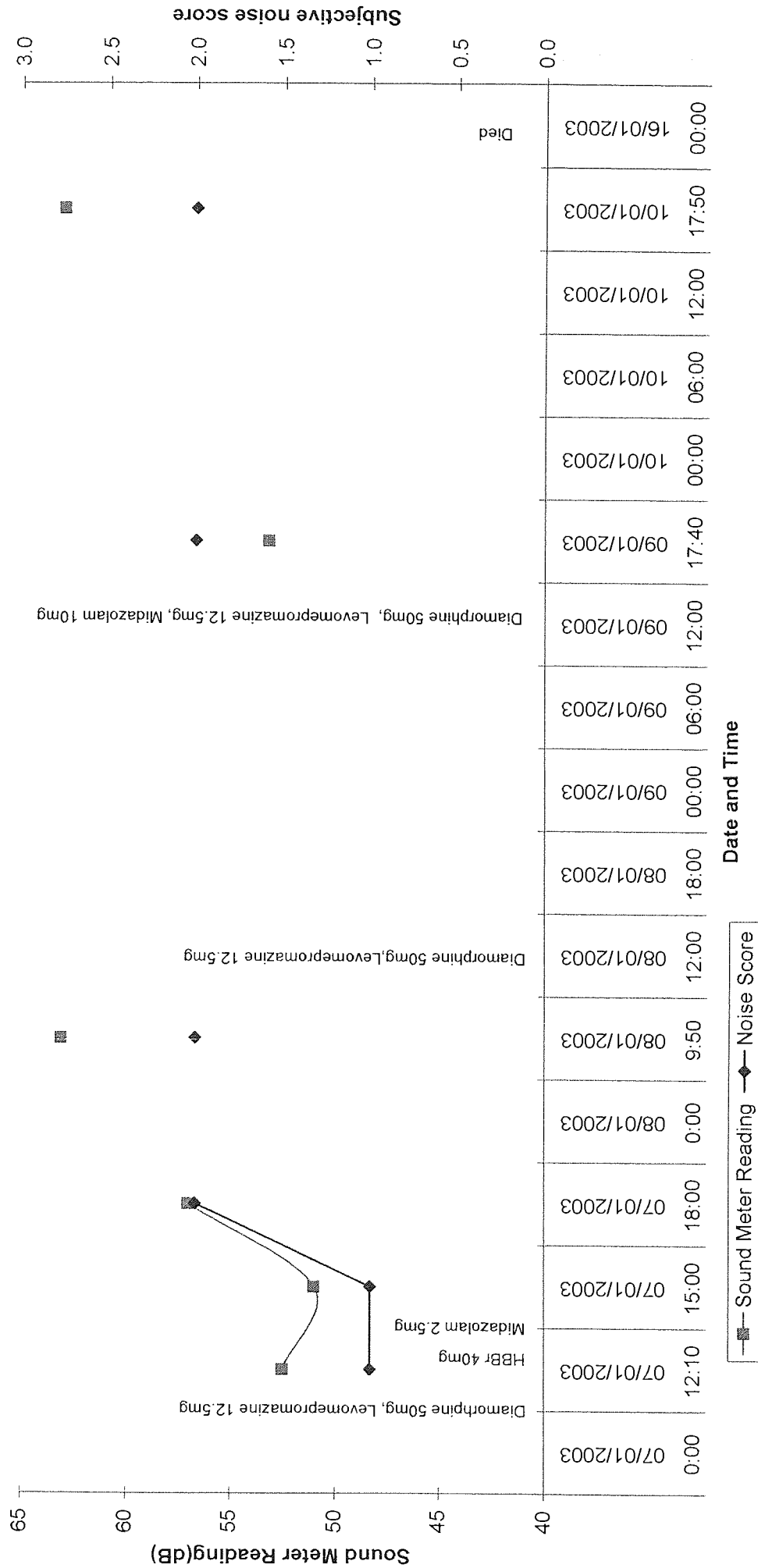
Case Profile SM105	Diagnosis of neurofibromatosis, Merkel cell carcinoma excised from right arm and leg.
Relevant Past Medical History	On admission the patient was chesty and physiotherapist was assisting expectoration
Study entry /consent issues	None
Concomitant medication	Bolus diamorphine, midazolam and clonazepam injection plus diamorphine infusion via a syringe driver with HBBr. A second syringe driver administered ketamine and midazolam.
Treatment for noisy breathing	A syringe driver of 120mg HBBr, together with a bolus injection GLY 400mcg. Suctioning was also performed.
Noise monitoring notes	Only three noise meter readings were taken during the study. A study entry the HBBr syringe driver had been running for eight and a half hours and two bolus injections of GLY had been administered. When the last bolus GLY injection had been administered, the noise meter reading was 56dB and the subjective score 3. Thirty minutes after the injection the subjective score remained at 3, the noise meter reading had increased by 4 dB. The nursing notes in the medical records recorded that greater effect had resulted from suction performed, although no noise level monitoring was done. The secretions were noted to be very thick and formed lumps. GLY was noted to have little effect.
Adverse effects	Secretions were noted to be thick and lumpy.
Other comments	The patient had been receiving subcutaneous infusions of drugs without anticholinergics prior to study entry.

Case Profile SM105



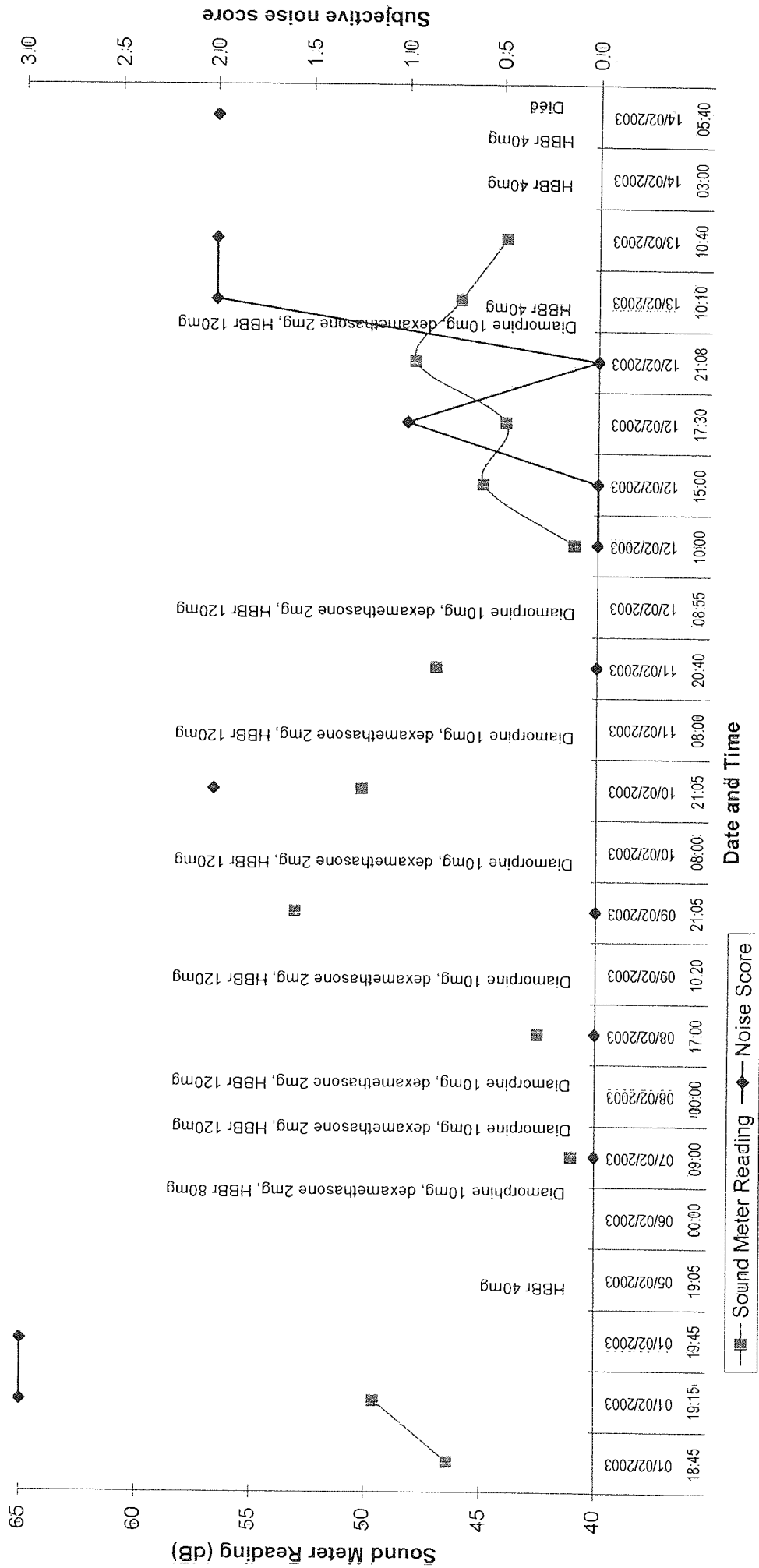
Case Profile . SM106	A 79 year-old female with cholangiocarcinoma
Relevant Past Medical History	Nothing of relevance
Study entry /consent issues	None
Concomitant medication	Diamorphine, levomepromazine and midazolam was administered via a syringe driver plus a bolus midazolam injection and one dose of oral morphine.
Treatment for noisy breathing	One bolus injection HBBr 40mg.
Noise monitoring notes	Patient was nursed in a single room. Two hours and 50 minutes after HBBr 40mg the subjective noise score was the same (1) but the noise meter reading had reduced by 1.5 dB. Five hours and 50 minutes later, when the next noise meter reading was taken, subjective score was 2 and the noise meter reading 57dB. No further medication was given. The next noise meter reading of 55dB corresponded with a subjective noise score of 2. Subsequently a subjective noise score of 2 was assigned corresponding to noise meter readings of 63dB , 53.2dB and 63dB showing poor correlation.
Adverse effects	None noted
Other comments	No documentation in patient's medical records of death rattle or its treatment.

Case Profile SM106



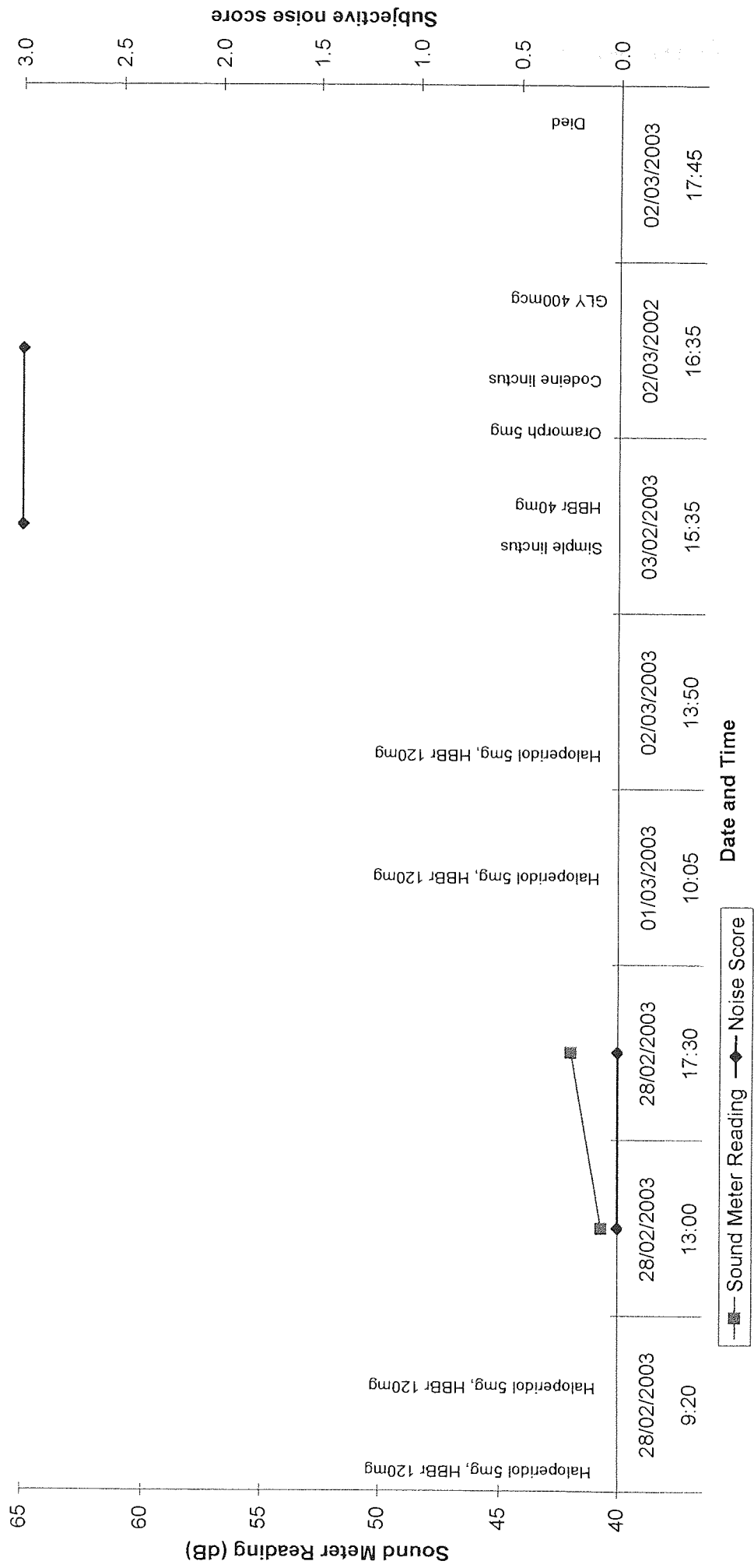
Case Profile SM107	A 65 year-old female with glioblastoma multiforme..
Relevant Past Medical History	None noted
Study entry /consent issues	None noted
Concomitant medication	Subcutaneous infusion of diamorphine, dexamethasone and HBBr. Also 'as required' oral doses of Oxycodone . Salbutamol (nebulised). Oral medication was still being taken during the present study: ranitidine, thyroxine, paroxetine, senna, lactulose. Regular medication was stopped on 9/2/03.
Treatment for noisy breathing	Bolus HBBr injection 40mg, then a syringe driver was added administering HBBr 120mg over 24 hours, with subsequent HBBr bolus injections of 40mg. Three bolus injections were administered at the end of the study period in addition to the syringe driver. The time between these injections was 5 hours and 2.5 hours respectively.
Noise monitoring notes	The first HBBr injection was not given until day 5 of the study. The patient had previously had a subjective noise score of 3 with a corresponding noise meter reading of 46dB reducing to 49dB the result in the nursing notes reported to be given with 'good effect'. Subsequently on 6/2/03 the patient was noted to be 'bubbly on moving but not requiring extra medication'. No baseline noise recording was done prior to giving the first bolus injection of HBBr, The syringe driver was then commenced containing HBBr during which time noise meter recordings fluctuated between 41dB and 53dB with subjective noise scores of zero, only peaking once to a score of 2. Nursing notes recorded 'Chest remains clear' on 7/2/03. The noise scores taken 24 hours after the syringe driver was set up with 120mg HBB was 41dB(noise meter) and 2 (subjective noise score). The peak noise meter reading (53.1dB) was subjectively scored at zero. This peak on 9/2/03 was at the time the patient was noted to have had 'soup in the throat' then reported to have cleared with a cough. No change in the anticholinergic medication was noted at this point to account for any decrease in noise levels. No bolus injections of HBBr were given until 13/2/03 when 'chestiness' was reported again in the nursing notes. The administration of HBBr 40mg bolus injection was recorded to have 'some effect'. The subjective noise score however remained at 2, the noise meter reading decreased by 4dB. However, the noise meter reading had already reduced by the same amount from the previous reading before the injection was given. No noise meter readings were taken for the last two injections but the last subjective score was still 2. The nursing notes that the 'bubbliness was not felt to be bothering the patient'. Chestiness increased further on 14/2/03 HBB felt to have 'reasonable' effect.
Adverse effects	None noted
Other comments	In the patients medical records the patient was noted to be rattly 'despite Buscopan [HBBr] and re-positioning, but not distressed.' Prior to death

Case Profile SM107



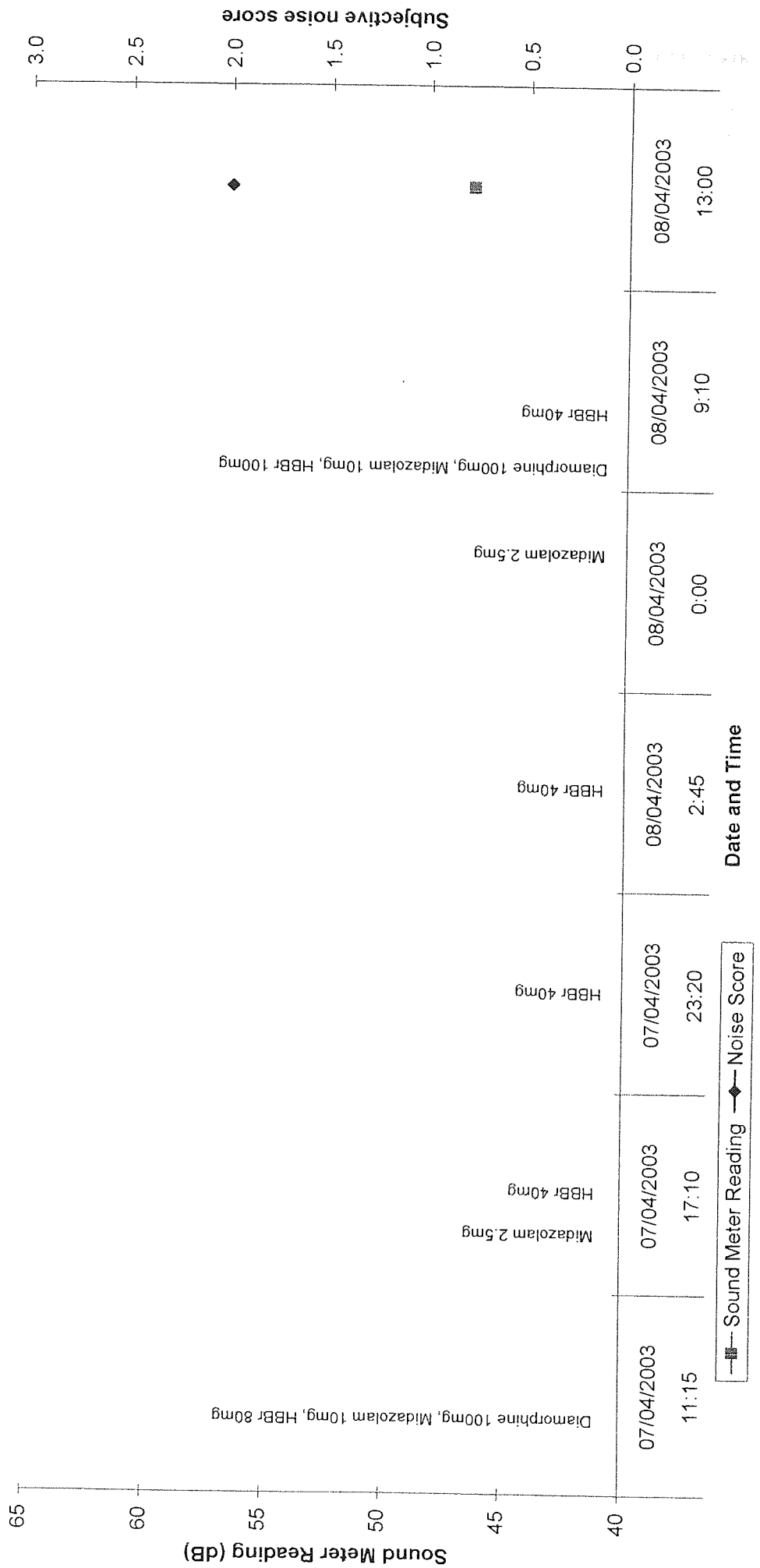
Case Profile SM108	A 79 year-old lady with ovarian carcinoma
Relevant Past Medical History	The patient had been admitted from hospital with problems of shortness of breath, difficulty expectorating and had received a recent course of intravenous antibiotics for pneumonia. The patient had symptoms of nausea and vomiting. The patient had ascites.
Study entry /consent issues	None noted
Concomitant medication	Receiving continuous oxygen via nasal specs. A syringe driver administered haloperidol with HBB. Oral morphine, simple linctus and codeine linctus were also given.
Treatment for noisy breathing	Frequent repositioning, (not documented on the chart). HBBr 120mg over 24 hours was administered via subcutaneous infusion, supplemented with one bolus injection of HBBr 40mg near the end of the study period and subsequent blous injection of GLY 400mcg.
Noise monitoring notes	A syringe driver with HBBr 120mg together with haloperidol 5mg had been started the day before entry into the study and was continued. A bolus dose of HBBr 40mg had also been given on 26 th , 2 days before entry into the study. The first monitoring was done just over 24 hours after the HBBr 120mg in the syringe dirver had been initiated. The noise level score was 0 and noise meter scores were 40.7dB and 42dB during this period. No further monitoring was done for two days until 3 rd February when a subjective noise score of 3 was recorded. A persistent irritating cough was recorded which did not respond to various measures including stat HBBr 40mg, Oral morphine 5mg, codeine linctus and finally GLY 400mcg stat. No outcome was recorded of this final injection.
Adverse effects	None recorded
Other comments	The patient did have a nasogastric tube in situ which came out on 28 th . The patient was reported to be breathless when lying flat.

Case Profile SM108



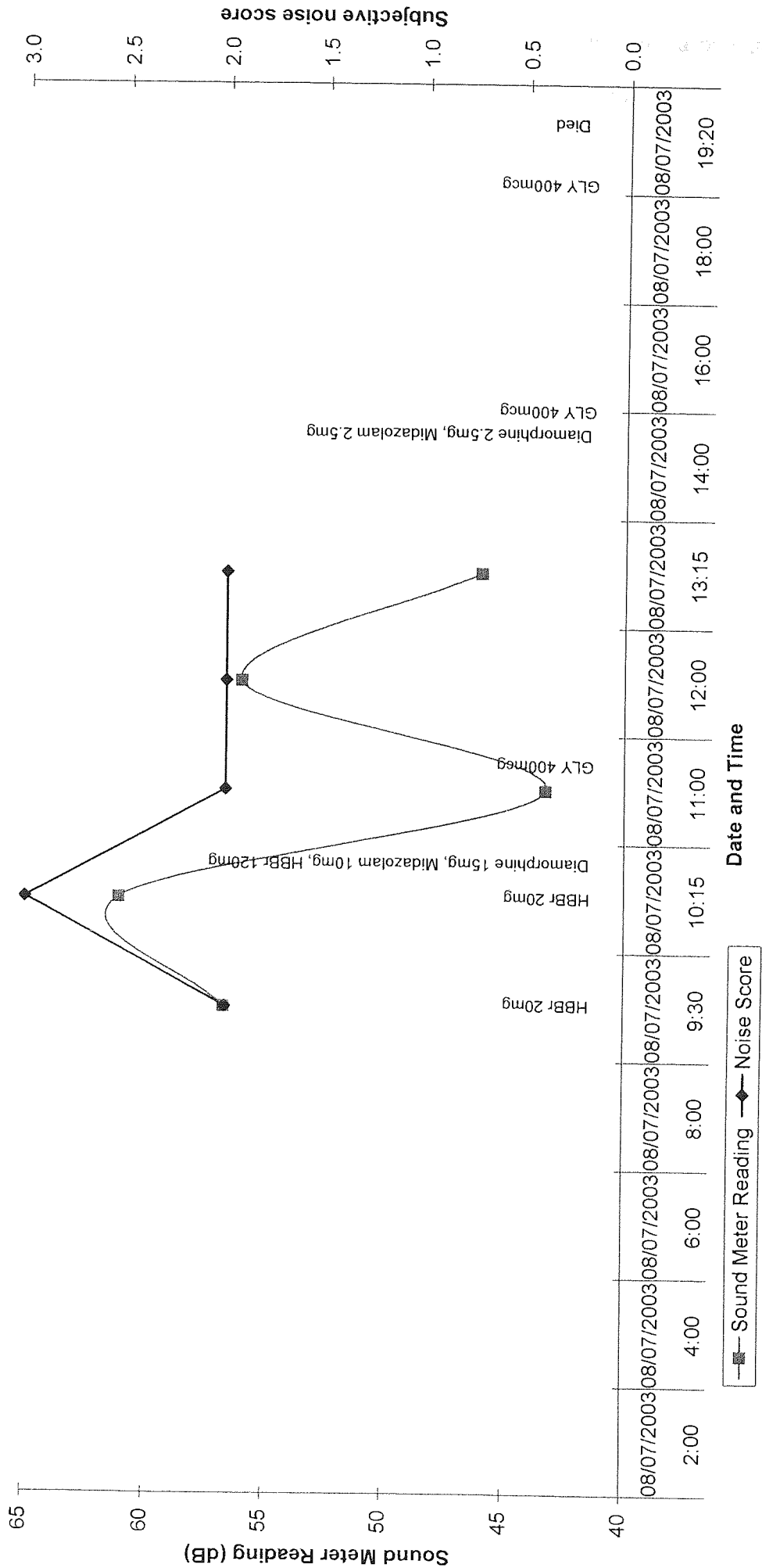
Case Profile SM113	A 65 year-old man with cancer of the tonsils and lung metastases.
Relevant Past Medical History	Patient was admitted requiring oxygen and shortness of breath when trying to speak. Previous sputum culture had revealed heavy growth of <i>Klebsiella pneumoniae</i> , a course of trimethoprim was prescribed. Nebulised bronchodilators were also used
Study entry /consent issues	None
Concomittant medication	Diamorphine and midazolam were administered over 24 hours by subcutaneous infusion together with HBBr. Bolus doses of midazolam were administered. Salbutamol was nebulised.
Treatment for noisy breathing	HBBr via subcutaneous infusion 80mg was then increased to 100mg over 34 hours, plus bolus injections of HBBr 40mg.
Noise monitoring notes	Only one point of monitoring was carried out, at the end of the study period. A noise score of 2 , with a noise meter reading of 46.5dB was recorded
Adverse effects	Nothing was recorded on the data collection sheet but nursing notes in the medical records reported that the patient had not passed urine 12 hours after starting HBBr infusion.
Other comments	After each injection of HBBr 'given with good effect' was noted in the patients medical records.

Case Profile SM113



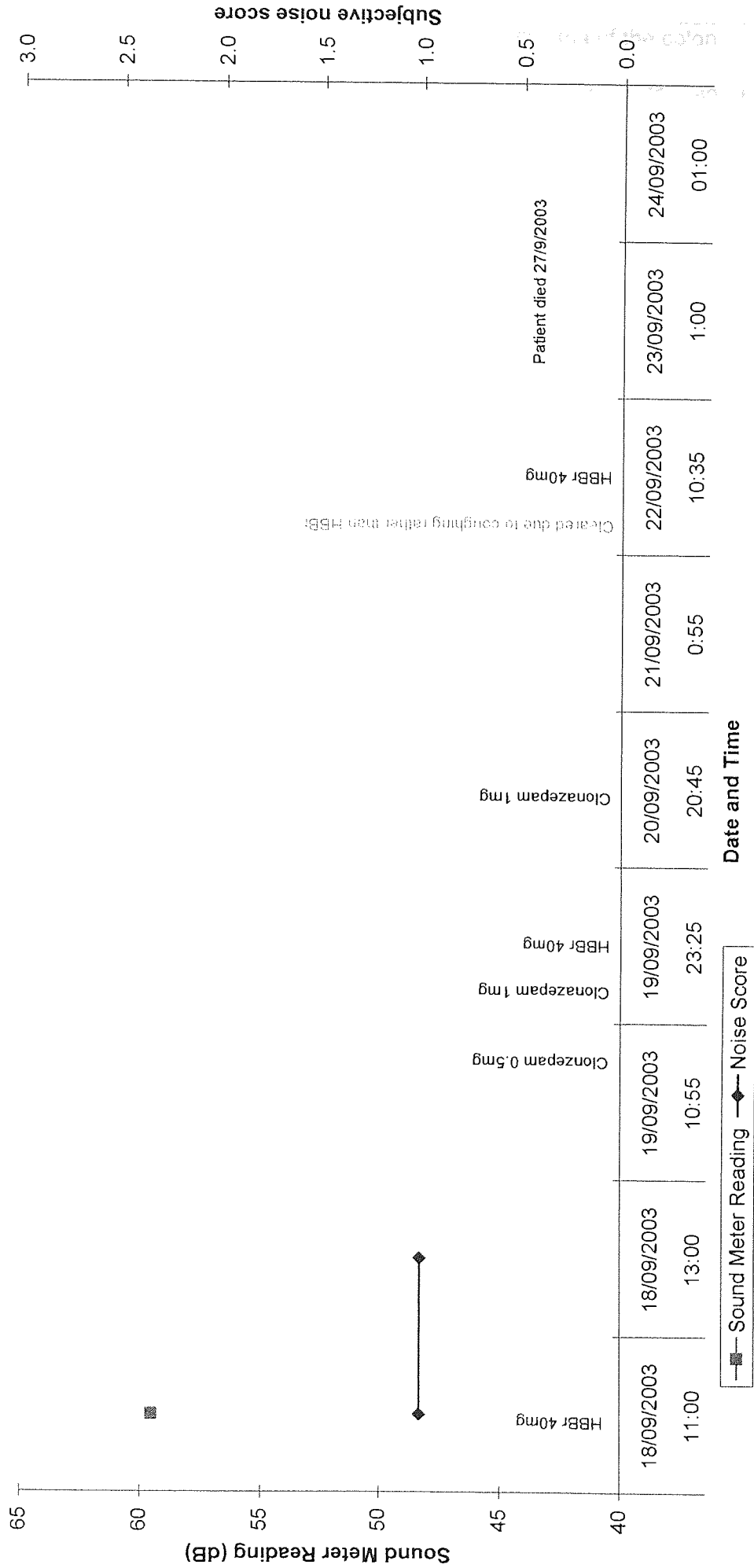
Case Profile SM115	A 71 year-old female with metastatic carcinoma of unknown primary
Relevant Past Medical History	A nasogastric tube in place on admission, was discontinued as became blocked and meals were refused. Only sips of fluid were being consumed.
Study entry /consent issues	None noted
Concomitant medication	Diamorphine and midazolam was administered via a syringe driver with HBBr during the study monitoring period. Bolus injections of diamorphine and midazolam were given after monitoring had been carried out but before death.
Treatment for noisy breathing	Two bolus HBBr injections of 20mg were administered, followed by HBBr 120mg in syringe driver (with diamorphine and midazolam) by subcutaneous infusion over 24 hours. Bolus injections of GLY 400mcg were administered. The time between the two GLY injections was just over three hours and 50 minutes but no monitoring was done to show the response to this.
Noise monitoring notes	One high noise meter reading thought to be due to a relative talking during the monitoring (noted by nursing staff), although this corresponded to a high subjective noise score. Forty five minutes after the first stat HBBr injection, the noise meter reading increased by 4.4dB . A further bolus injection followed by initiation of syringe driver with diamorphine, midazolam, HBBr and 45 minutes later noise meter reading had decreased (noting the possibility that the high reading may have been spurious). The subjective noise score also decreased to 2 at this point. The subjective noise score remained at 2 but the noise meter reading increased, returning to a similar level (46dB) three hours later. No further readings were taken.
Adverse effects	None noted
Other comments	The nasogastric tube which had been in place was discontinued owing to patient having difficulty clearing their throat. The administration of two further bolus injections of GLY indicate that noisy breathing was still a problem. 'Some effect' from these injections was noted by nursing staff in the medical records. It was also noted that patients family were present and very distressed. The patient was nursed in a multi-bedded bay.

Case Profile SM115



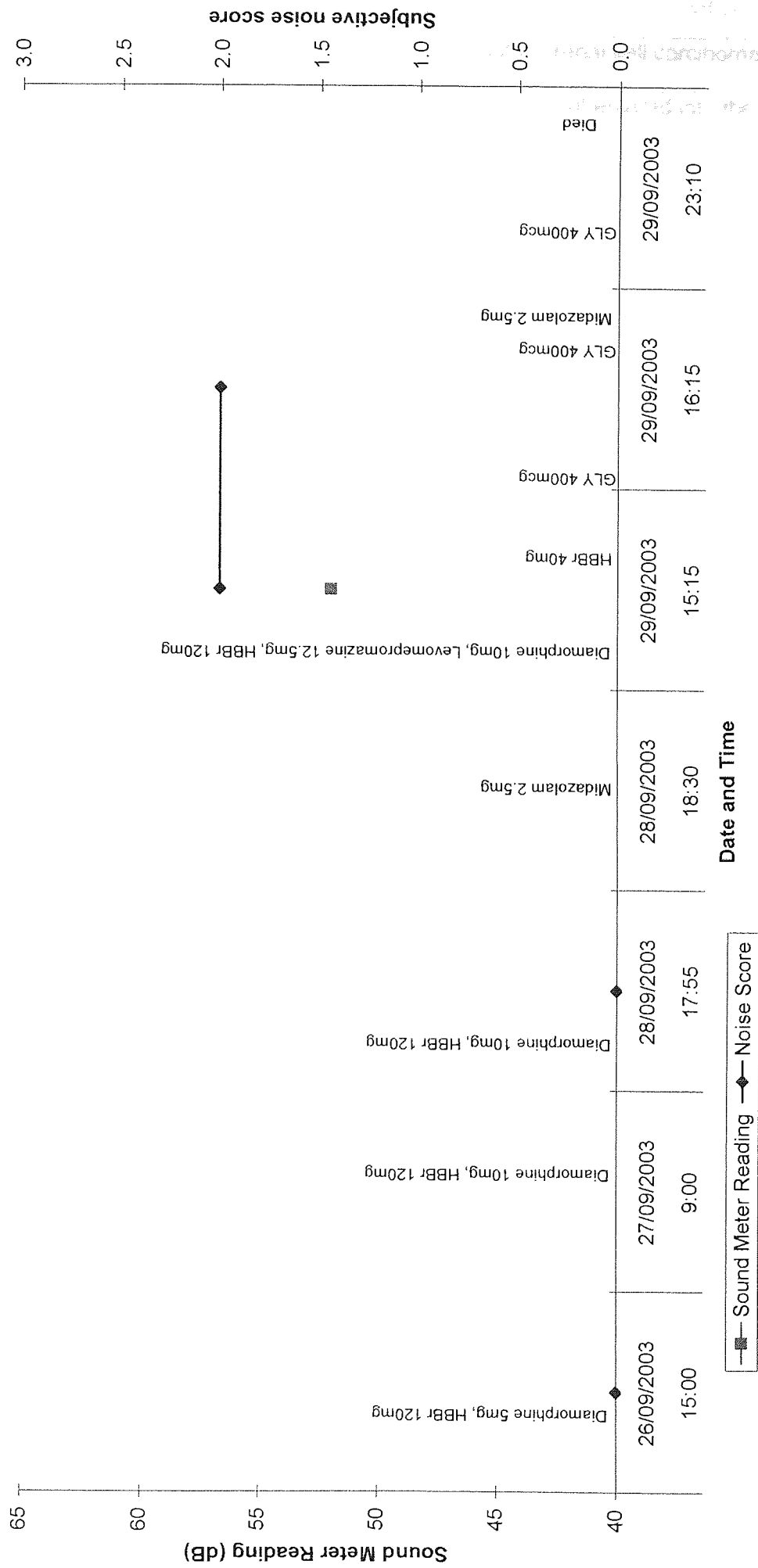
Case Profile . SM119	A 63 year-old female with carcinoma of the left parotid gland with local and lung metastases
Relevant Past Medical History	The patient had received radiotherapy to the parotid area. The patient had a history of hypertension. Subcutaneous fluids were administered. A urinary catheter was in situ.
Study entry /consent issues	None noted
Concomitant medication	Diamorphine, midazolam and levomepromazine were administered by subcutaneous infusion over 24 hours. Clonazepam was administered by bolus injection . Dexamethasone was continued, given by bolus injection. Prochlorperazine, pantoprazole and senna was given orally daily during the study period. Subcutaneous fluids were given for thirst.
Treatment for noisy breathing	Three bolus injections of HBBr 40mg were given during the study period. One had been given prior to the study period
Noise monitoring notes	Only one noise meter reading was taken of 59.5dB when a bolus injection of HBBr was administered, corresponding to a subjective noise score of 1. The subjective noise score remained unchanged two hours later. No further monitoring was done. When the second injection was administered, the noise score was noted to have improved, although not marked on the chart or score, but was attributed to the patient coughing rather than the HBBr injection
Adverse effects	None recorded
Other comments	Nursing staff recorded in the medical records that the 'chestiness' could have been due to aspiration of thickened drinks

Case Profile SM119



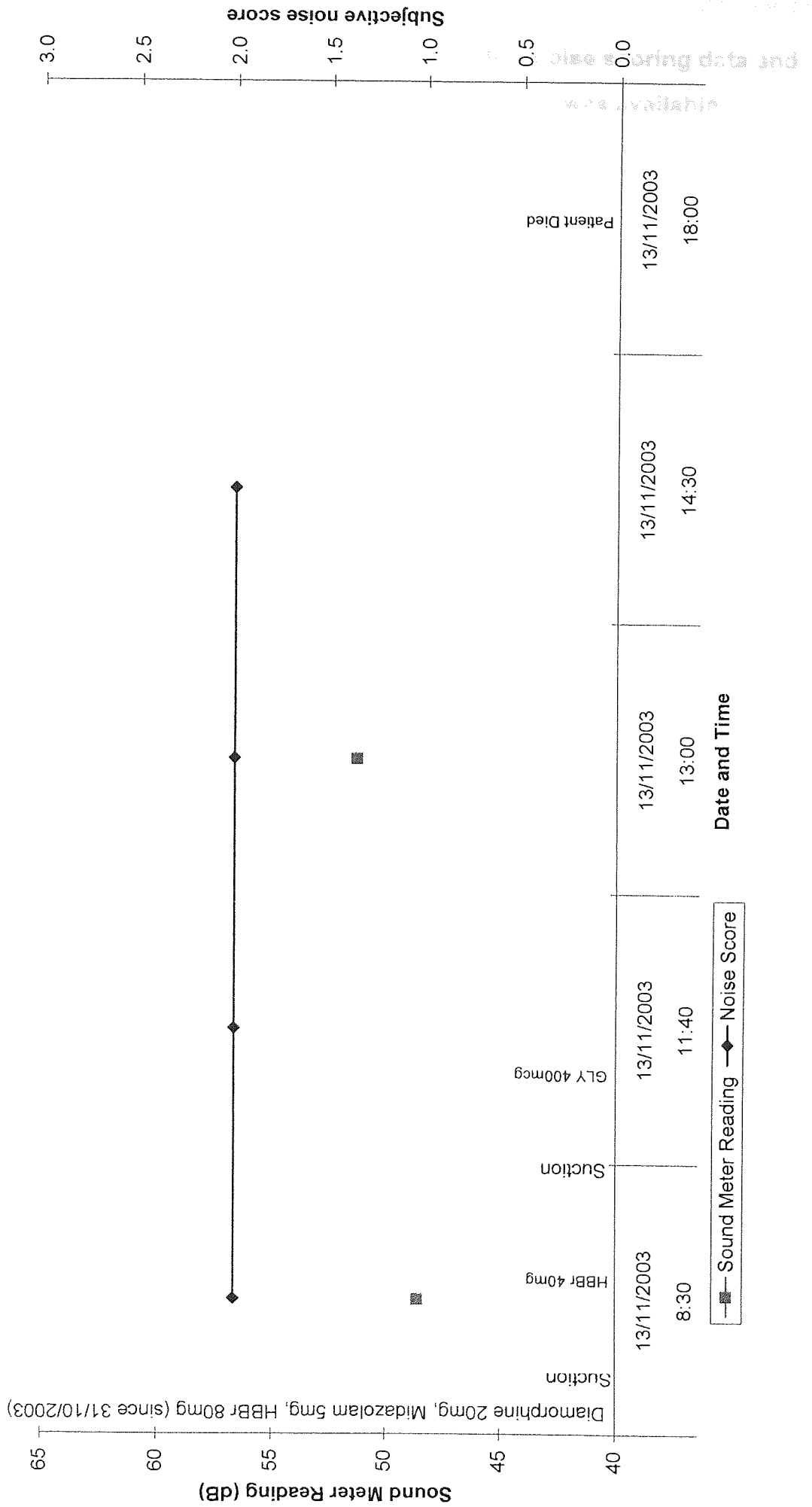
Case Profile SM120	A 71 year-old with metastatic carcinoma of the colon.
Relevant Past Medical History	Problems on admission included previous ascites, anorexia and fatigue.
Study entry /consent issues	None noted
Concomitant medication	Bolus injections of midazolam were administered. Levomepromazine was added to the existing syringe driver the syringe driver on 29 th September.
Treatment for noisy breathing	A syringe driver administered HBBr 120mg then bolus injections of HBBr and GLY. The first GLY injection was given 1 hour after the HBBr injection, the second GLY injection was administered n 3 hours 25 minutes later and the third, three and a half hours later again.
Noise monitoring notes	No noise monitoring was carried out until the end of the study period for this patient, then one noise meter reading of 52dB, corresponded to a subjective noise score of 2. Until that time the subjective noise score had been zero with HBBr 120mg infusion. The subjective noise score remained at 2 after the bolus HBBr and GLY injections were administered. Nursing notes in the patients medical records note the patient being 'a bit rattly' despite Buscopan' (HBBr) and later on 29/9/03 as being 'very rattly' therefore glycopyrronium given'. It was noted on 30/9/03 remains poorly and bubbly, glycopyrronium given with little effect.'
Adverse effects	None noted
Other comments	None noted

Case Profile SM120



Case Profile SM121	A 53 year-old female with metastatic renal cell carcinoma
Relevant Past Medical History	Patient was consented on 7/10/3 but not entered into the study or monitored until 13/11/03
Study entry /consent issues	None noted
Concomitant medication	A syringe driver with diamorphine, midazolam and HBBr had been initiated before noise monitoring had been carried out. Oral medications which continued until 13/11/03 were dexamethasone, lansoprazole, co-danthramer, senna and lactulose.
Treatment for noisy breathing	HBBr 80mg had been included in the syringe driver for several days (since 29/10/03) Stat doses of HBBr 40mg had been given prior to study entry, one dose was subsequently given on 13/11/03 and four hours later bolus GLY 400mcg was administered together with suction.
Noise monitoring notes	Although in the notes suction was recorded as having some effect, the subjective noise score remained at 2 throughout the monitoring period. No change was noted after either bolus injection. No improvement was recorded in the medical records. The noise meter readings were not consecutive and were 48.6dB when the HBBr bolus injection was given and 51dB three hours and twenty minutes after GLY was given.
Adverse effects	Nothing recorded on the chart but in notes, patient recorded as having dry mouth.
Other comments	Secretions were considered to be a problem for this patient but felt most distressing for the family. Views of the relative were obtained.

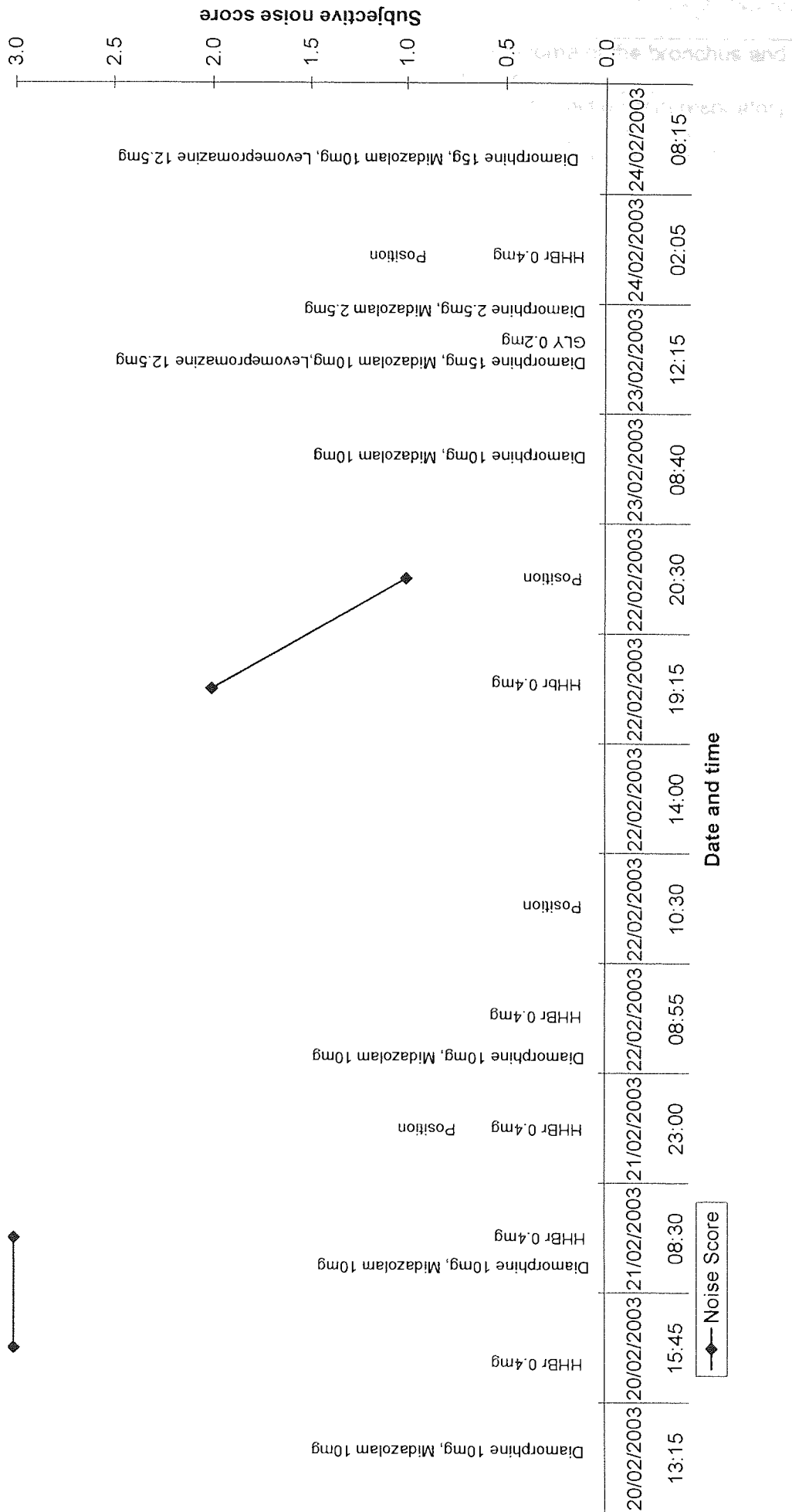
Case Profile SM121



Group 2 Patient case profiles where subjective noise scoring data and background data from the patients' medical records was available

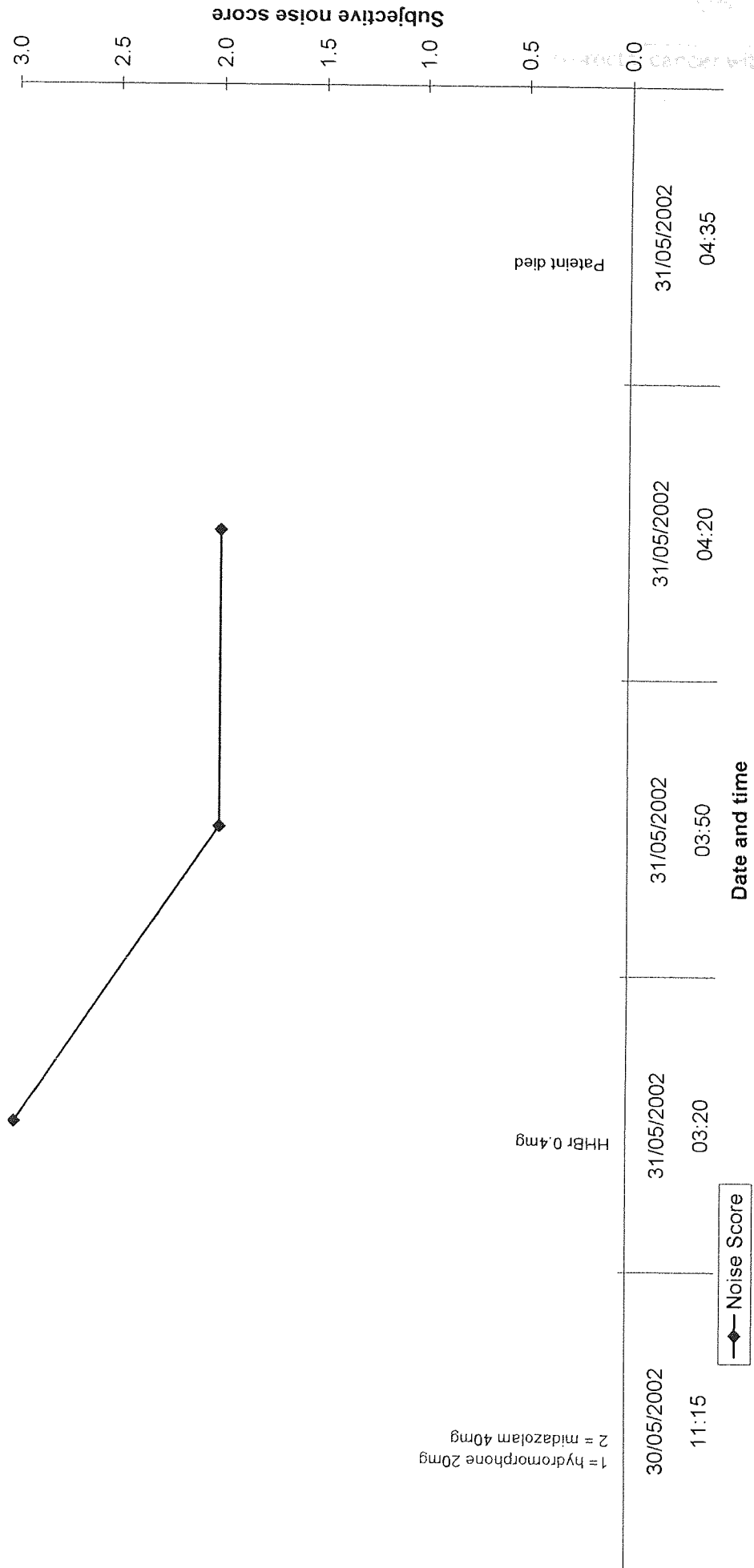
Case Profile C002	A 70 year-old male with carcinoma of the prostate
Relevant Past Medical History	The patient may have had a stroke causing left sided weakness
Study entry /consent issues	None noted
Concomitant medication	A syringe driver with diamorphine and midazolam was being administered, later levomepromazine was added and bolus midazolam injection.
Treatment for noisy breathing	Six bolus injections HHBr 0.4mg were administered followed by, bolus GLY 200mcg. A bolus injection of HHBr was administered. The patient was nursed on 30 degree tilt and position change was noted.
Noise monitoring notes	The subjective noise score was three when the first two HHBr 0.4mg bolus injections were administered. The second reading was taken nearly 17 hours after the first and therefore could not be directly compared. The only consecutive subjective noise score readings were after the fifth injection of HHBr where the patient was given, however nursing medical records report that the patient remained 'bubbly and chesty'. The doctors medical records for 23 rd report that the patient was 'rattly' and confused and 'Hyoscine not effective against rattle'.
Adverse effects	None noted
Other comments	GLY was noted in the patients notes not to be any better than any other agent. Confusion was noted in the notes but not recorded on the data collection chart. The nurses noted that hyoscine was given and effective but the patient was still chesty –'chestiness' was also noted to be better when the patient was repositioned. The problem persisted and GLY was given to see if it was any more effective than hyoscine, however a dose of 200 microgram was chosen when 400 microgram of hysocine had been given previously '

Case profile C002



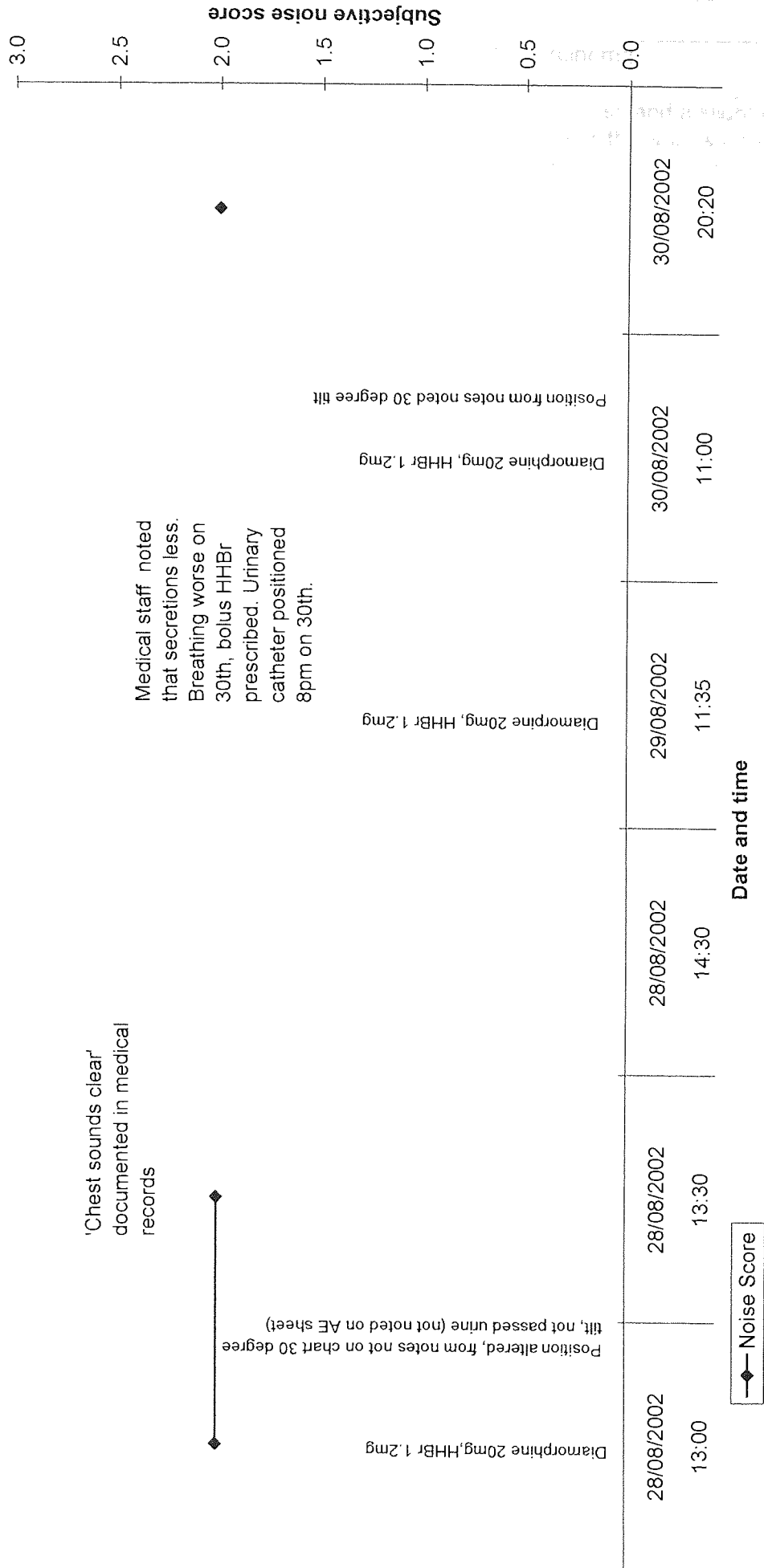
Case Profile C003	A 52 year-old male with adenocarcinoma of the bronchus and metastases in spinal cord and brain.
Relevant Past Medical History	He was noted to have a recent chest infection with respiratory secretions on admission, and was taking the inhaled bronchodilator ,salmeterol and steroid inhaler flixotide for an underlying chest condition. Problems on admission were noted to be urinary retention and dry mouth, together with opioid toxicity.
Study entry /consent issues	None noted
Concomitant medication	A subcutaneous infusion of hydromorphone and midazolam was also given. Simple linctus given for tickly cough.
Treatment for noisy breathing	One bolus injection of HHBr 0.4mg
Noise monitoring notes	The subjective noise score reduced from 3 to 2 thirty minutes after the HHBr 0.4mg injection was administered and remained at this level two hours later.
Adverse effects	None recorded
Other comments	None recorded

Case profile C003



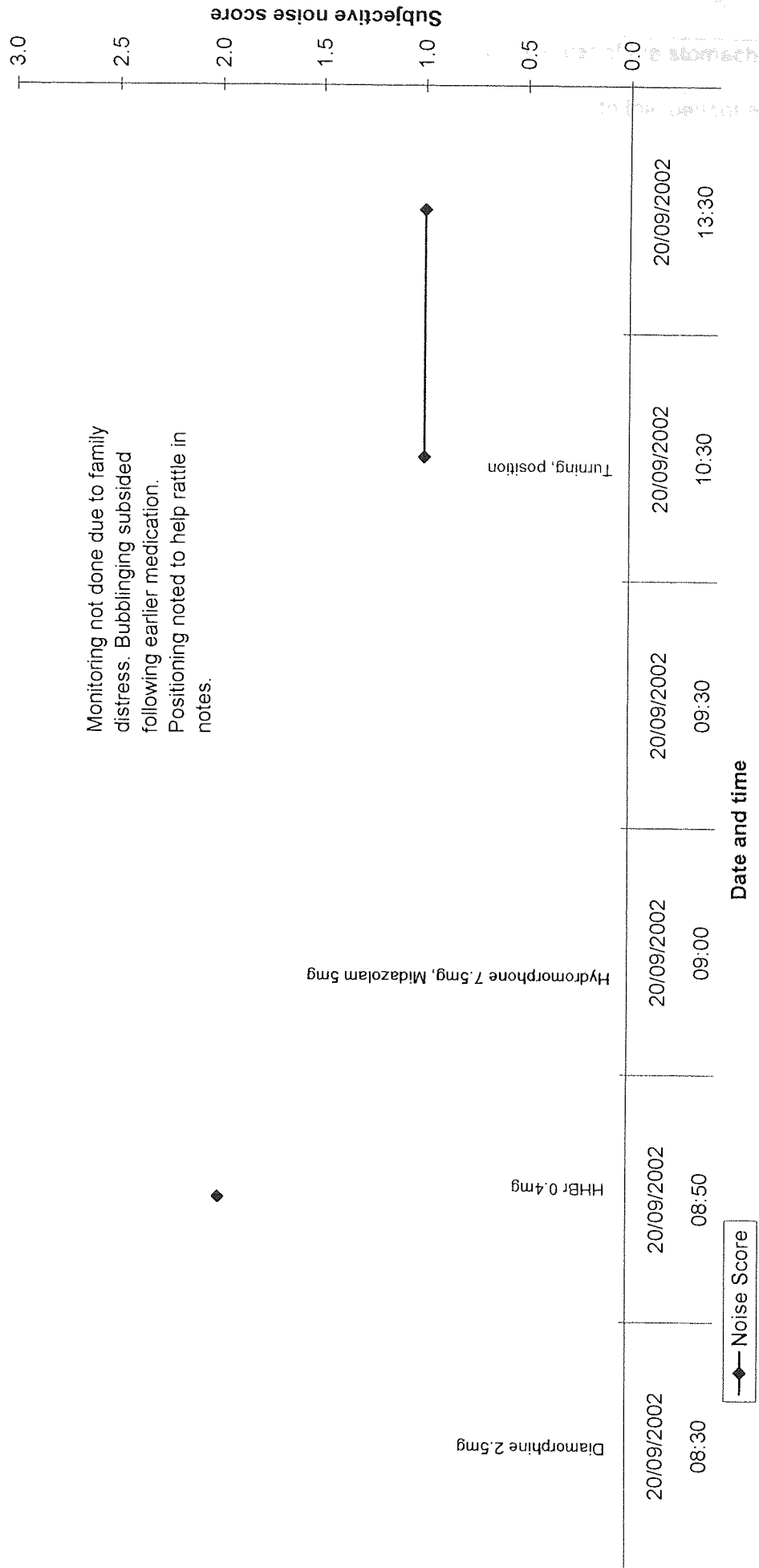
Case Profile C007	A 67 year-old male with metastatic colorectal cancer with liver metastases.
Relevant Past Medical History	None noted
Study entry /consent issues	This patient had received medication via a syringe driver for three days including HHBr when entered into the study.
Concomitant medication	A subcutaneous infusion of diamorphine 20mg was also in the syringe driver with HHBr, given through the study period
Treatment for noisy breathing	This patient was nursed on a 30 degree tilt which was not noted on the form together with HHBr 1.2mg over 24 hours by subcutaneous infusion.
Noise monitoring notes	No record to explain lack of noise meter monitoring. Although only three subjective noise scores were noted, all noise scores were 2.
Adverse effects	The patient had a urinary catheter inserted. This was not recorded on the data collection form as a possible adverse effect. The patient had not passed urine for 48 hours. Also noted that catheter only drained minimal amount of concentrated urine.
Other comments	'Chest sounds clear' was recorded in the nursing notes at 11:00 on 29/8/02. On 30/8/02 'bubbly breathing was felt to be worse and blous doses of HHBr prescribed as needed. None were administered.

Case profile C007



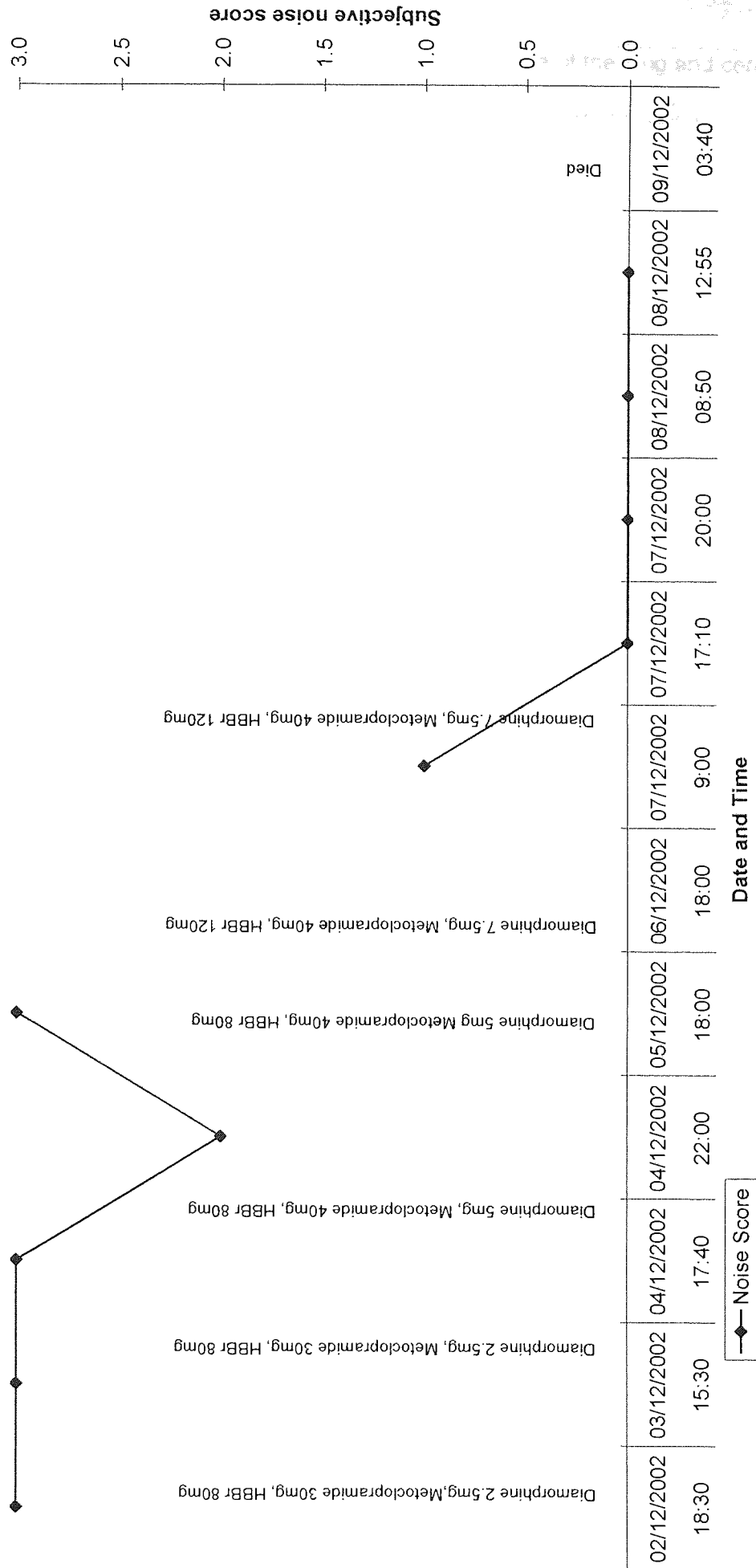
Case Profile C008	A 75 year-old male with prostatic carcinoma.
Relevant Past Medical History	Problems on admission included weakness and a slight cough with small amounts of phlegm. Trouble with swallowing was noted. A course of cephalexin had been prescribed previously, simple linctus was given for cough
Study entry /consent issues	None noted
Concomitant medication	Bolus diamorphine injection was administered for pain. A syringe driver with hydromorphone and midazolam was initiated at the same time as HHBr was given together with a bolus injection of diamorphine 2.5mg. Dexamethasone 4mg was administered bolus subcutaneous injection.
Treatment for noisy breathing	One stat injection HHBr 0.4mg given.
Noise monitoring notes	Subjectively the noise score decreased from 2 to 1 within 2 hours of the HHBr injection being administered. Positioning was noted to help the rattle in the patient's medical records, but not documented on the recording chart. Noise meter monitoring was not done due to family anxiety
Adverse effects	None recorded
Other comments	None recorded

Case profile C008



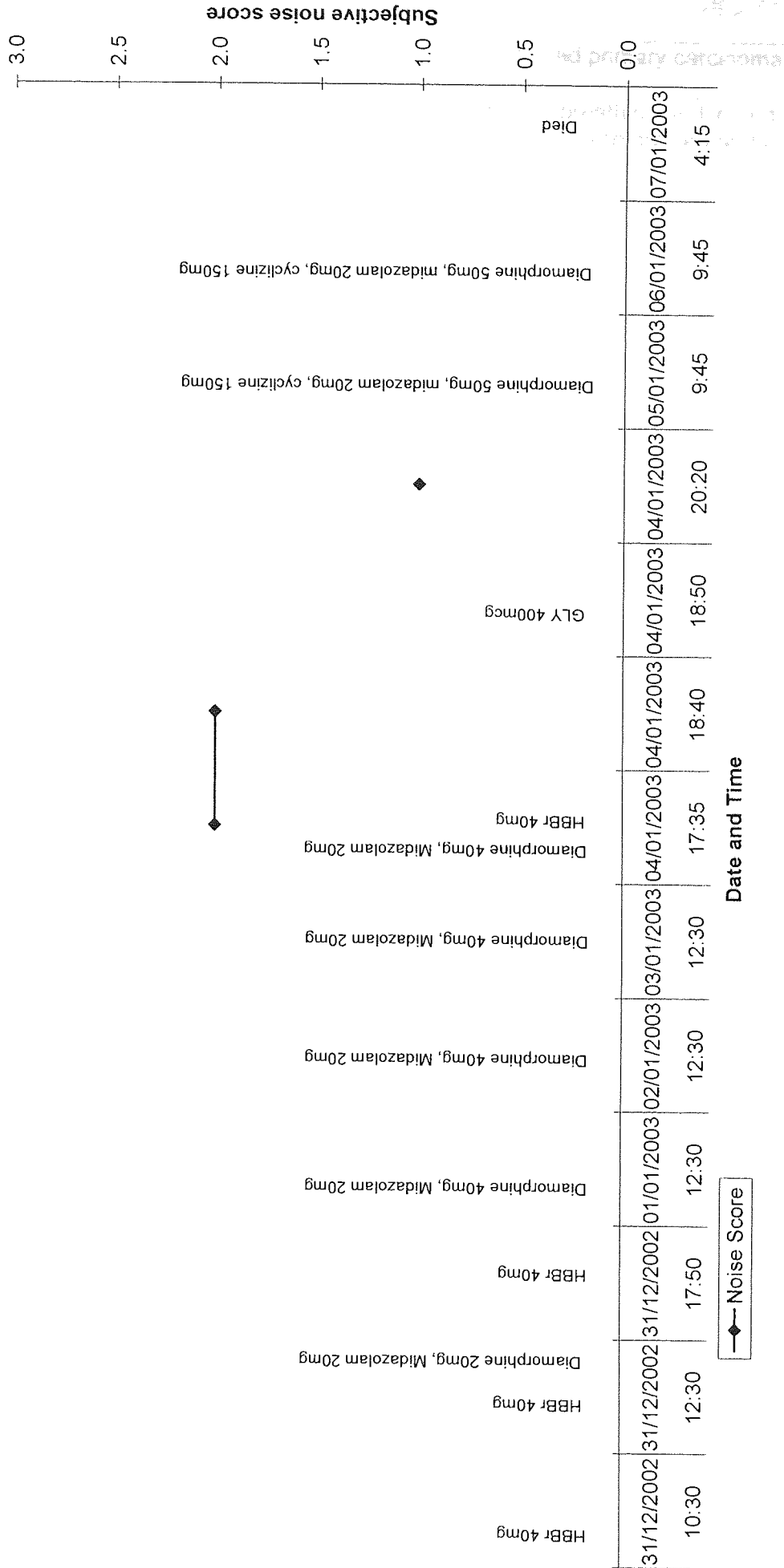
Case Profile SM101	An 86 year-old male patient with cancer of the stomach.
Relevant Past Medical History	Subcutaneous fluids were administered to this patient and continued throughout the study period.
Study entry /consent issues	None noted
Concomitant medication	Diamorphine 2.5mg and metoclopramide 30mg in syringe driver with HBBr
Treatment for noisy breathing	HBBr 80mg was administered by subcutaneous infusion over 24 hours in the syringe driver on 2/12/2. This was repeated daily until the 6 th when the HBBr dose was increased to 120mg. No bolus doses were administered.
Noise monitoring notes	The subjective noise score remained at 3 for the first two days, decreased to 2 on the fourth and then increased back to 3 on 5/12/02. After a break in monitoring, a score of one then reduced to zero for the rest of the study.
Adverse effects	None noted.
Other comments	At the beginning of the study nurses noted the patient 'sounds rattly in spite of Buscopan' and on 5/12/02 'chest sounds quite bubbly when asleep'. By 7/12/02 the patient was 'not sounding bubbly'

Case Profile SM101



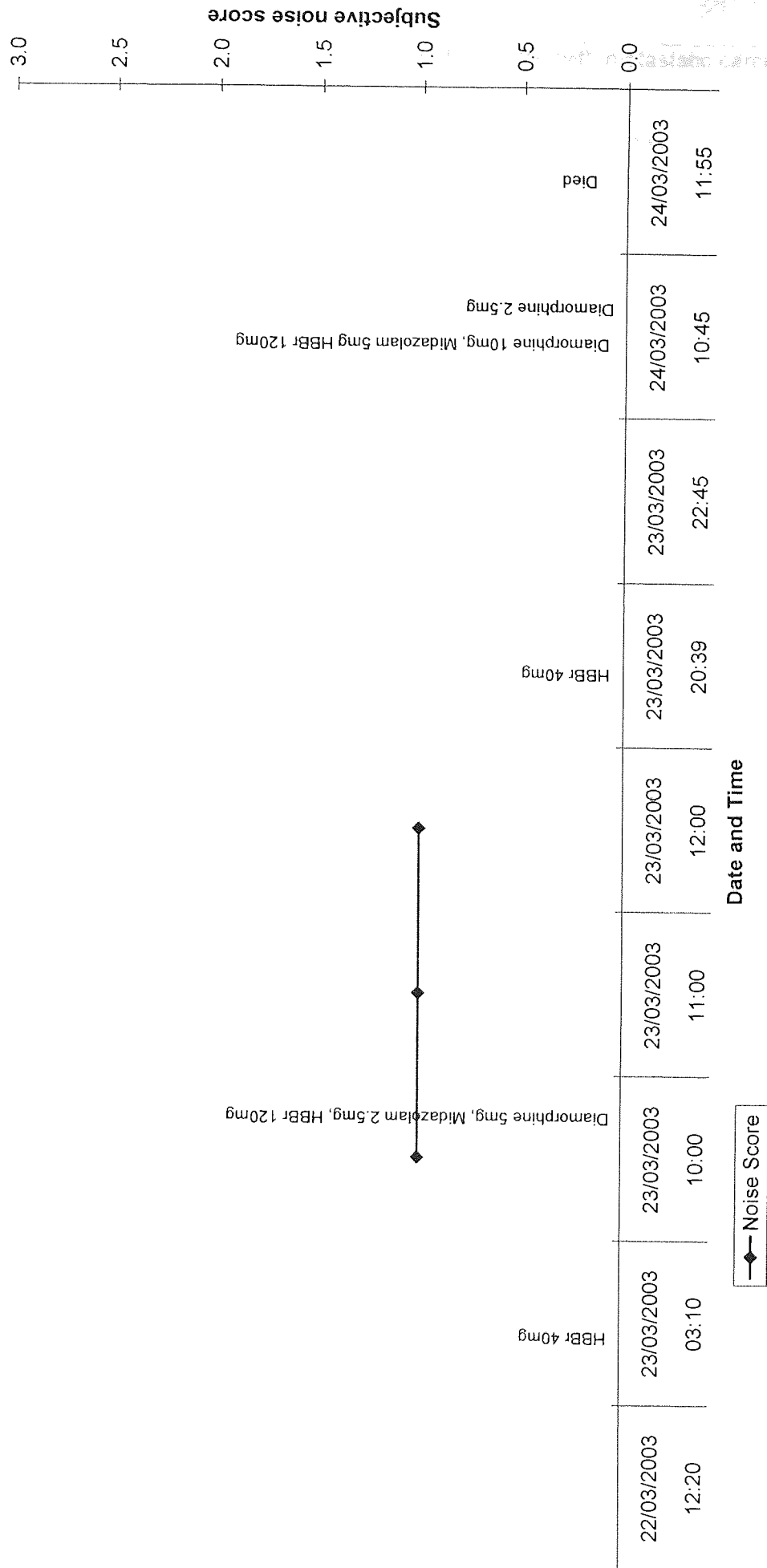
Case Profile SM 104	A 74 year-old female, with carcinoma of the lung and cerebral and liver metastases.
Relevant Past Medical History	Admitted with weakness, cough and slurred speech.
Study entry /consent issues	Too weak to give written consent but daughter consented on her behalf.
Concomitant medication	HBBr had been given for colicky pain until 4/1/03. A syringe driver administered diamorphine and midazolam subcutaneously over 24 hours. Cyclizine was later added to the syringe driver.
Treatment for noisy breathing	On 4/1/03 HBBr bolus 40mg was administered. Bolus GLY 400mcg also administered.
Noise monitoring notes	The bolus HBBr was noted to have made no improvement to 'bubbliness'. After administration of GLY it was noted that 'improved rattle greatly'. A subjective noise score of 2 reduced to 1, 1.5 hours after the bolus GLY injection.
Adverse effects	None noted
Other comments	It was noted in the medical records by medical staff ' to try HBBr for colicky pain and add to the syringe driver if effective.' There was also a note requesting glycopyrronium to be added to the syringe driver if it was effective.

Case Profile SM104



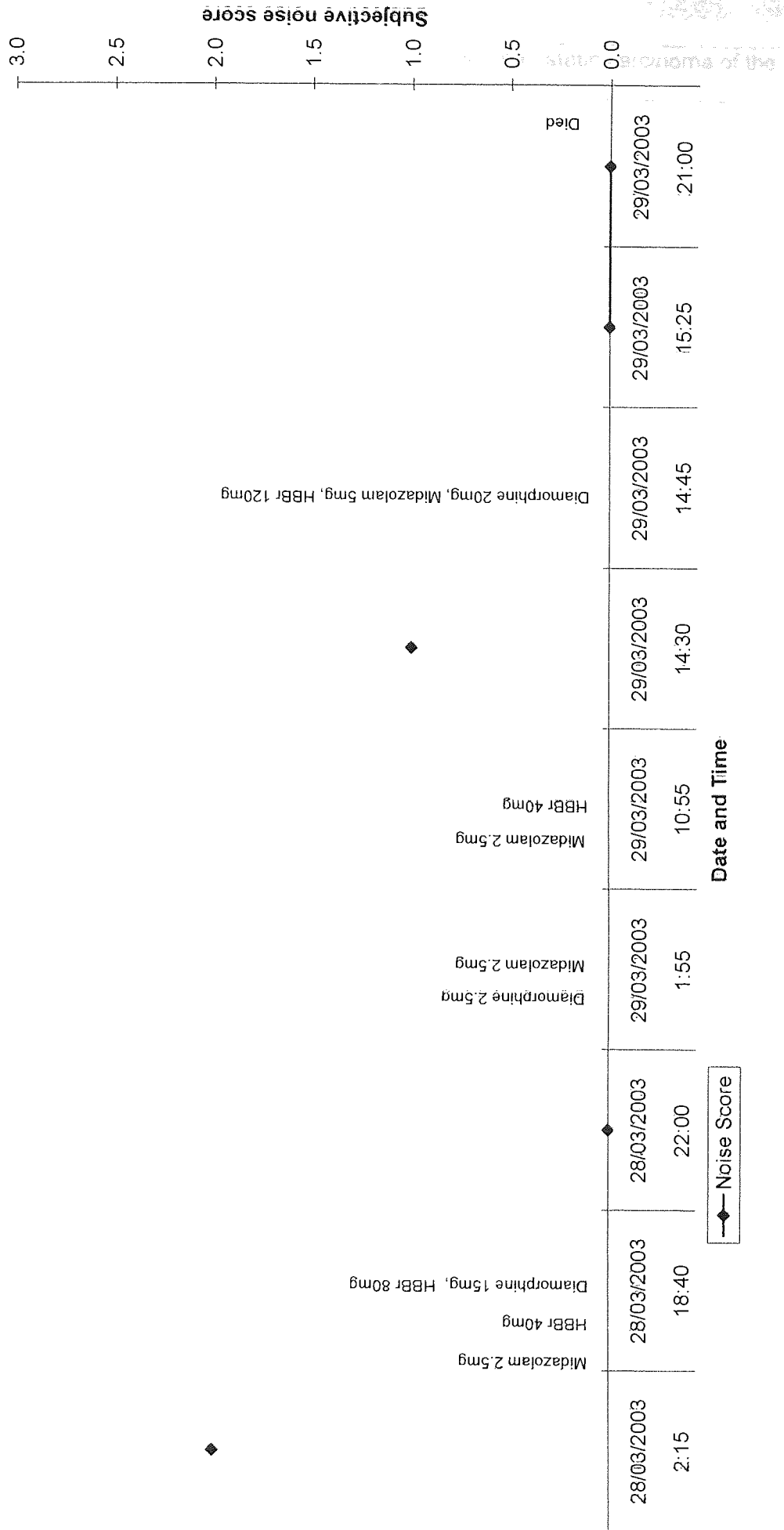
Case Profile SM109	A 90 year-old female with unconfirmed primary carcinoma of the ovary and lung metastases.
Relevant Past Medical History	Admitted from hospital with difficulty breathing and increasing shortness of breath. Pleural effusions were drained at the time of admission. A urinary catheter was in situ.
Study entry /consent issues	None noted
Concomitant medication	Syringe driver administering a subcutaneous infusion of midazolam and diamorphine with HBBr over 24 hours. Bolus injections of diamorphine were also administered.
Treatment for noisy breathing	Stat injection of HBBr 40mg, syringe driver containing HBBr 120mg administered over 24 hours.
Noise monitoring notes	Only three points of subjective monitoring were recorded with a noise level of 1 during the infusion and between injections of HBBr.
Adverse effects	None noted
Other comments	No nursing notes regarding effect of HBBr were made, although the second bolus injection HBBr was given because the patient was 'a little chesty'

Case Profile SM109



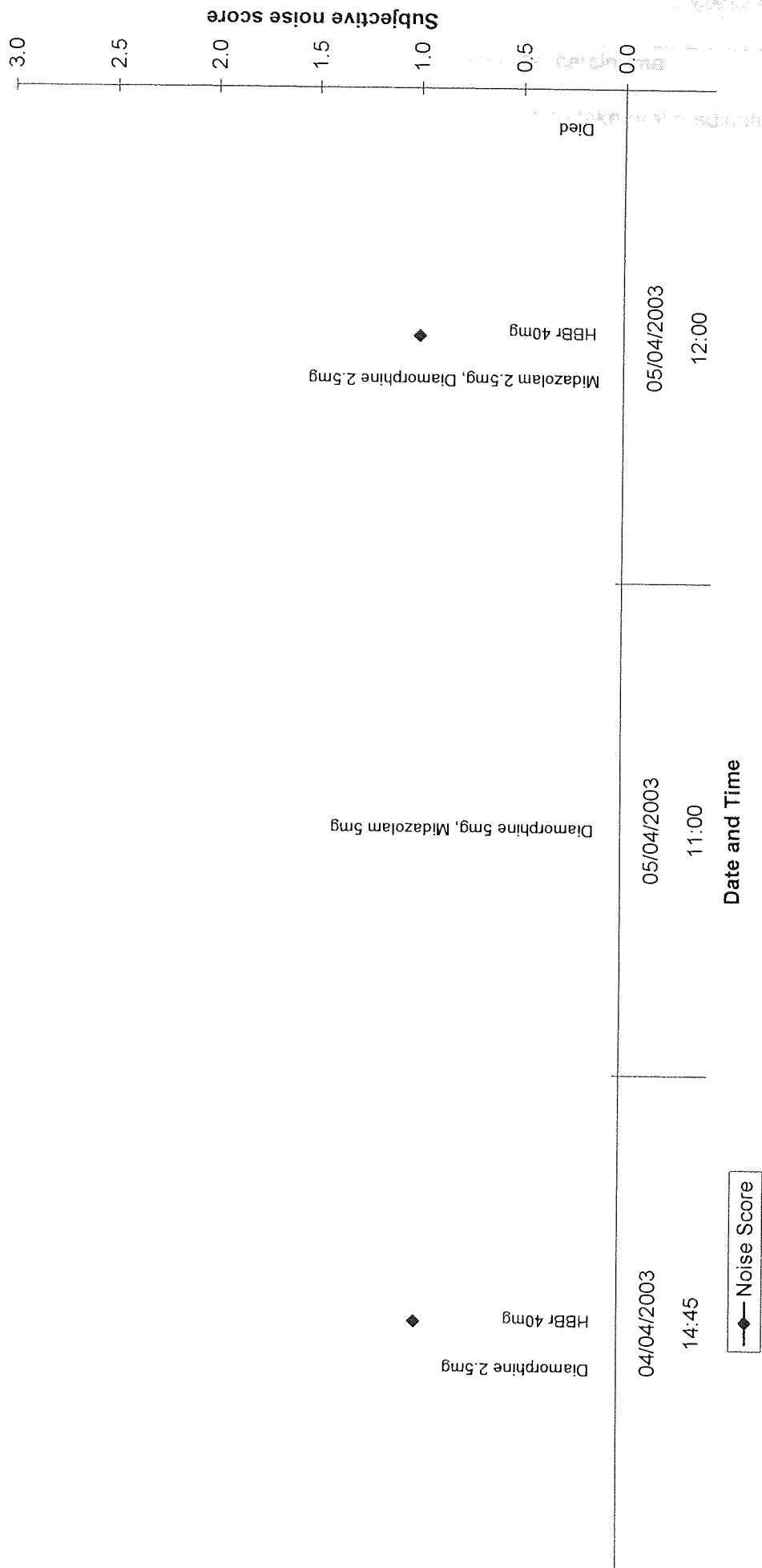
Case Profile SM110	A 73 year-old male patient admitted with metastatic carcinoma of the colon
Relevant Past Medical History	The patient had difficulty swallowing medicines
Study entry /consent issues	None noted
Concomitant medication	Bolus injections midazolam and diamorphine, plus a syringe driver with a subcutaneous infusion of diamorphine with HBBr, later including midazolam were administered.
Treatment for noisy breathing	Two bolus injections HBBr 40mg, plus a syringe driver with 24 hours subcutaneous infusion of HBBr 80mg then 120mg.
Noise monitoring notes	Subjective noise scores were initially 2. Three hours and 20 minutes after HBBr 40mg bolus together with 80mg HBBr administered via a syringe driver, the subjective noise score reduced to zero. A further stat HBBr 40mg was administered on 29/3/03. Three hours and 25 minutes later the subjective noise level was 1, but returned to zero by a further 55 minutes.
Adverse effects	None recorded, however urine had not been passed overnight of the 28/3/03 or by 29/03/03.
Other comments	The first bolus injection, was considered to be effective. HBBr was added to the driver. The perceived effect had been almost immediate. The second HBBr injection administered at the same time as midazolam was felt to have 'good effect', The syringe driver HBBr dose was increased to 120mg.

Case Profile SM110



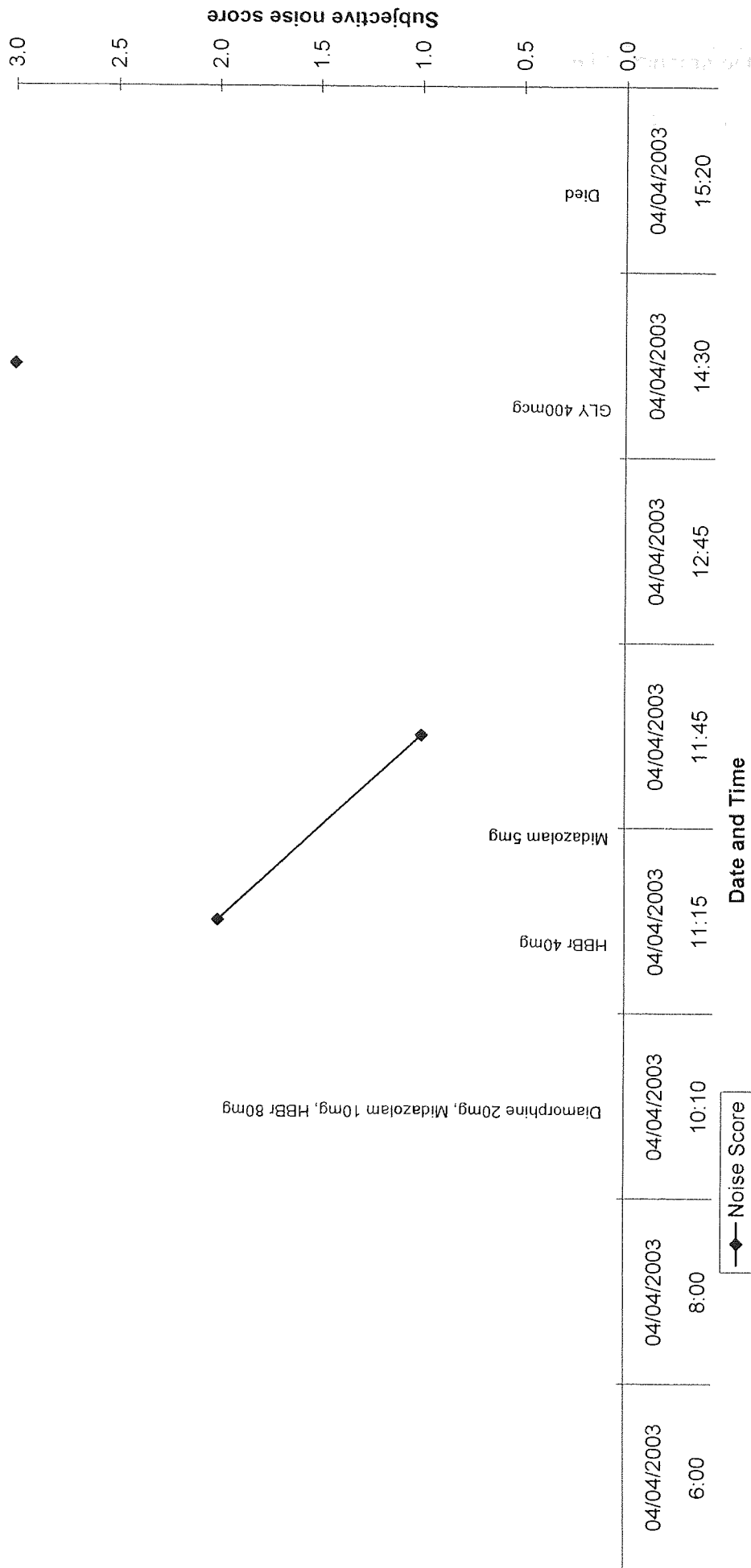
Case Profile SM111	A 96 year-old male patient with metastatic carcinoma of the prostate.
Relevant Past Medical History	None noted
Study entry /consent issues	None noted
Concomitant medication	Lactulose, senna, prednisolone, cyproterone, glimepiride,omeprazole. were being taken orally on 4/4/3. Plus bolus diamorphine and midazolam together with a syringe driver infusing diamorphine and midazolam subcutaneously over 24 hours
Treatment for noisy breathing	Two bolus doses of HBBr 40mg, 22 hours and 45 minutes apart.
Noise monitoring notes	Subjective noise scores were only monitored when the injections were administered and were scored at 1 each time. The second stat HBBr injection was given for 'chestiness' whereas the first may have been for colic, even though noise levels monitored.
Adverse effects	None noted
Other comments	None noted

Case Profile SM1111



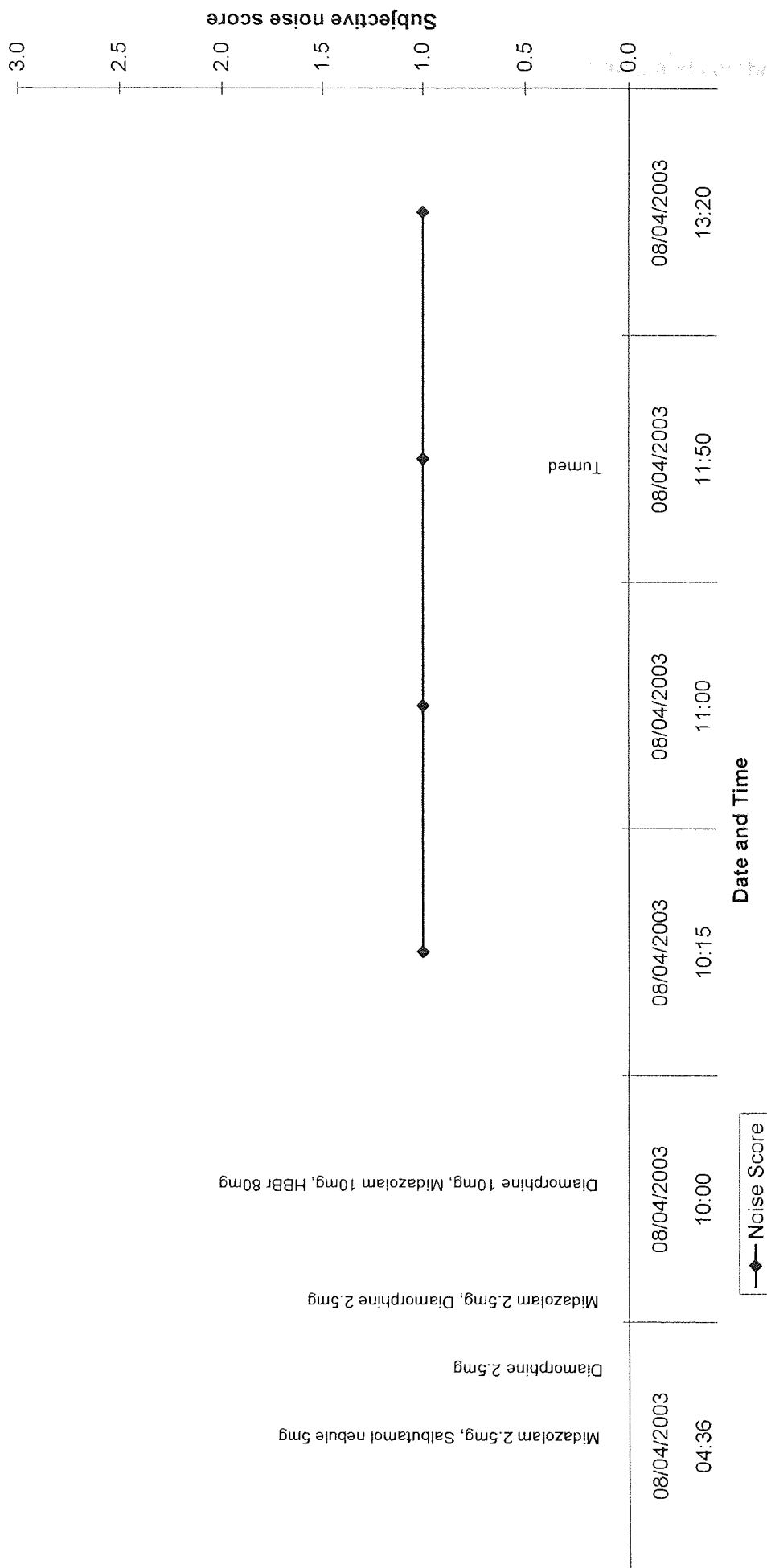
Case Profile SM112	A 52 year-old female with colorectal carcinoma.
Relevant Past Medical History	Consented by doctors when unable to take oral medications.
Study entry /consent issues	None noted
Concomittant medication	Diamorphine and midazolam by subcutaneous infusion by syringe driver over 24hours plus bolus midazolam were administered.
Treatment for noisy breathing	HBBr 80mg in syringe driver, bolus HBBr then bolus GLY 400mcg
Noise monitoring notes	Three subjective noise scores were recorded. A score of 2 reduced to 1, 30 minutes after HBBr was given. A subjective noise score of 3 was recorded at the same time that GLY was administered. Nursing staff notes indicated that HBBr in the syringe driver helped 'for a while 'Midazolam was also given. There was no record of effectiveness of GLY.
Adverse effects	None noted
Other comments	None noted

Case Profile SM112



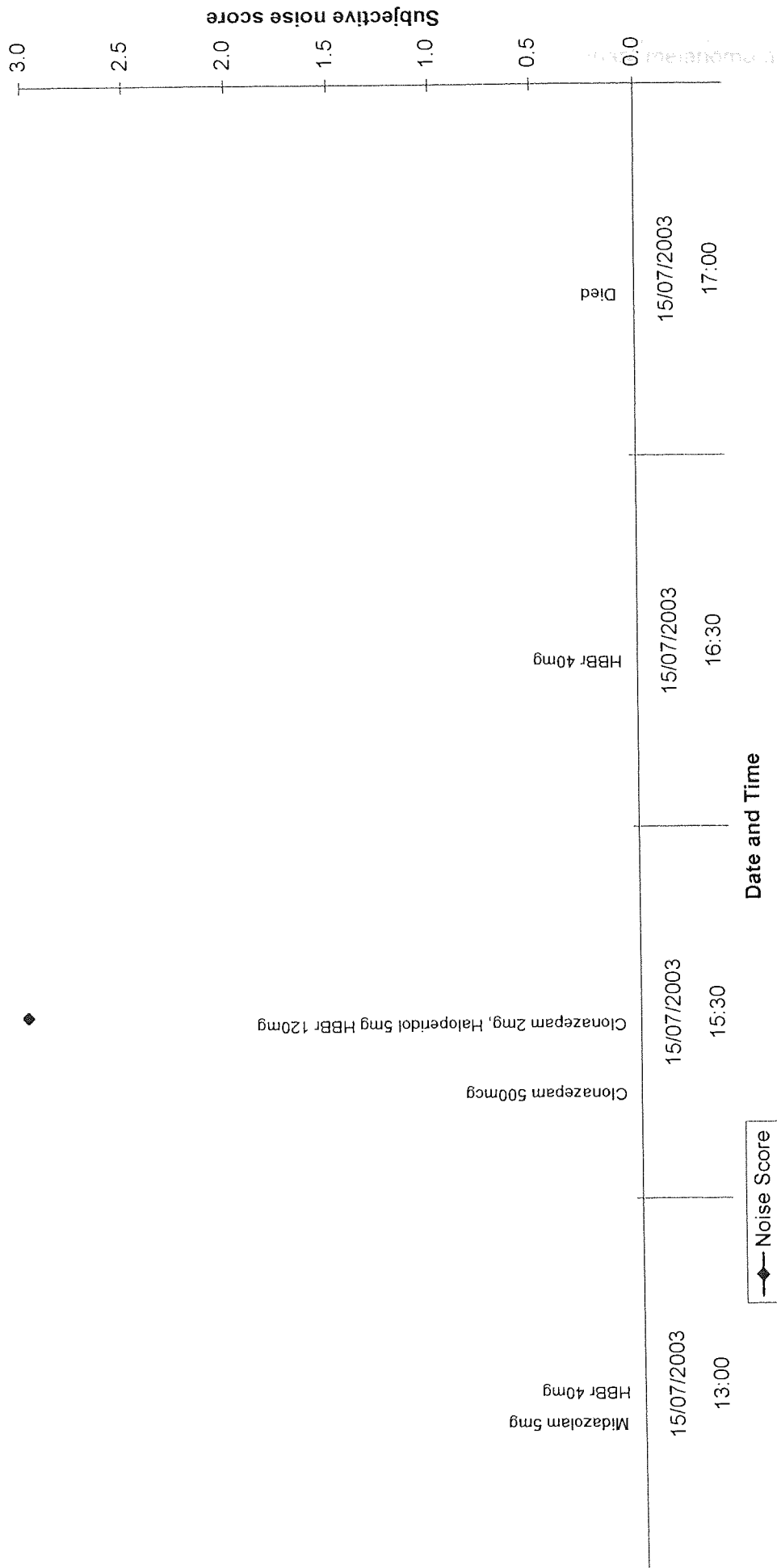
Case Profile SM114	A 74 year-old patient with non small cell carcinoma of the lung with renal failure due to metastases.
Relevant Past Medical History	The patient had a history of asthma and was prescribed regular beclometasone dipropionate inhaler (Beclazone) and combined ipratropium/ salbutamol inhaler (Combivent). A course of antibiotics was prescribed for suspected urinary tract infection, this was stopped at the time of entry into the study. Subcutaneous fluids were administered.
Study entry /consent issues	None noted
Concomitant medication	Salbutamol was nebulised 'with effect'. Bolus midazolam and diamorphine were administered together with a syringe driver infusing diamorphine and midazolam subcutaneously over 24 hours with HBr.
Treatment for noisy breathing	HBr 80mg subcutaneously over 24 hours
Noise monitoring notes	Subjective score only recorded a noise level of 1 over the last three hours of the study.
Adverse effects	None noted
Other comments	None noted

Case Profile SM114



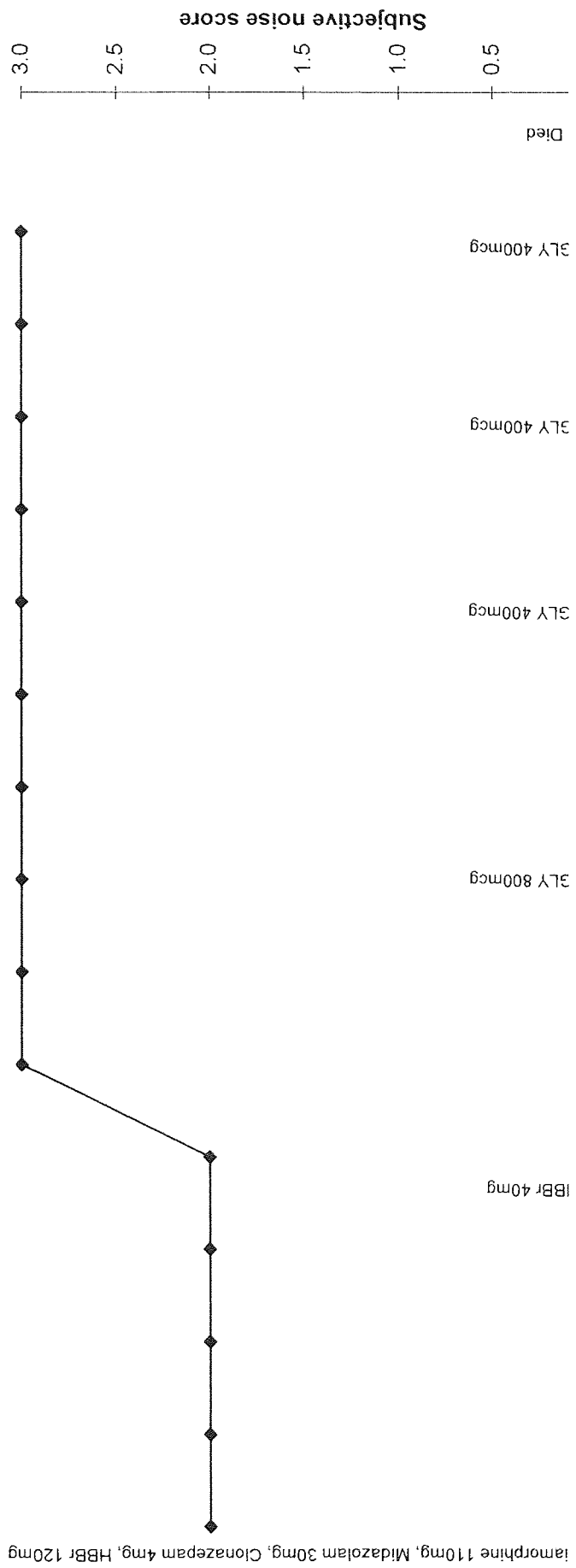
Case Profile SM116	A 60 year-old lady with carcinoma of the lung and cerebral metastases
Relevant Past Medical History	None noted
Study entry /consent issues	Patient unresponsive, consent via daughter.
Concomitant medication	Bolus midazolam, bolus clonazepam plus syringe driver administering clonazepam and haloperidol with the HBBr.
Treatment for noisy breathing	Two bolus injections HBBr 40mg plus 120mg HBBr added to the syringe driver. Suction was performed at the same time as the bolus injection was administered.
Noise monitoring notes	Only one monitoring point was recorded at 3. When the first bolus HBBr was administered 'some effect' was noted in the nursing notes of the patients medical records.
Adverse effects	None recorded
Other comments	None recorded

Case Profile SM116



Case Profile SM117	A 68 year-old male with metastatic malignant melanoma admitted for pain control
Relevant Past Medical History	The patient had a urinary catheter in situ.
Study entry /consent issues	The doctor who took consent for this patient had been anxious about consenting the patients for the study, but found that in this patient that the process had not been difficult. The patient was short of breath on admission to hospital, continuous oxygen was maintained via nasal specs. There was no record of when this was stopped.
Concomitant medication	During the study period the syringe driver administered diamorphine, midazolam, clonazepam and HBBr
Treatment for noisy breathing	The syringe driver contained 120mg HBBr and was infused subcutaneously over 24 hours. A bolus dose of HBBr 40mg was administered 6 hours and 50 minutes later. Bolus GLY 400mcg was then administered 70 minutes later, repeated after 4 hours and 20 minutes, 1 hours and 50 minutes and 3 hours and 55 minutes.
Noise monitoring notes	Only subjective monitoring was carried out. An initial score of 2 was made at the start of the study. The subjective noise score rose to three and HBBr was given. The score remained at 3, no improvement being recorded in response to bolus doses of HBBr or GLY. HBBr was noted to have 'no effect' in nursing notes.
Adverse effects	None noted.
Other comments	Agitation was a main problem for this patient, which was noted to be distressing for the daughters present. No reason given for not using noise meter.

Case Profile SM117



Died

SLY 400mcg

SLY 400mcg

SLY 400mcg

SLY 800mcg

IBR 40mg

ibuprofen 10mg, Midazolam 30mg, Clonazepam 4mg, HBR 120mg

Case Profile SM118	A 62 year-old male with metastatic
Relevant Past Medical History	None noted
Study entry /consent issues	None noted
Concomitant medication	Diamorphine and clonazepam was subcutaneous infusion in a syringe HBBr. Paracetamol 1 dose was given midazolam and clonazepam
Treatment for noisy breathing	Turning was performed and recorded 120mg HBBr added to the syringe 100mcg and HBBr 400mcg were given
Noise monitoring notes	Although noise monitoring was started during the longest time period for any patient injections of HBBr and adding HHI noise score was 2 at 25 minutes after 1 hour. The noise score remained zero. The next bolus injection of HBBr coinciding with a subjective noise score was zero at next monitoring 12 hours. The patient was turned frequently throughout on the data collection period. Although no high noise readings were recorded, the prescribed drug to HBBr was made. A noise score of 2 resulted in GLY being given 24 hours later, followed quickly by a noise score of 2. Notes in the patient's medical records noted 'movement momentarily'. The fluctuating rattle continued throughout the study. GLY may have been of some effect.
Adverse effects	None noted.
Other comments	Although breathing was felt to have improved after administration on 7 th , it was recorded that there may have been some chestiness. Nursing on patient's side was noted 'chestiness'.

Group 3 Patient case profiles where background data and medical records only was available

Case profile C001	A 75 year-old female with carcinoma of
Relevant Past Medical History	None noted
Other Comments	The patient was consented but not monitored. It was stated that there was no noise to monitor and no sputum given for secretions that could not be collected. Not enough information documented in the notes to know whether the hyoscine had been effective. The patient previously had pleural effusions, was using salbutamol, bronchodilators and on diuretics. She was on 20mg of HBr.

Case profile C014	A 53 year-old female with non small cell carcinoma
Relevant Past Medical History	None noted
Other Comments	No monitoring was done but over 4 day trial of anticholinergic injections were given twice daily with little effect as then GLY 200mcg was given. No further anticholinergics were then administered. When within 6 hours 20mg HBr was given. GLY . A syringe driver was then initiated on 80mg. Carer interview 'No objective benefit' was seen with HBr. Secretions persisted, further drugs were given. The patient also received doses of midazolam for anxiety. Ipratropium nebulas were also used. Sputum.

Case profile C016	A 71 year-old patient with carcinoma of
Relevant Past Medical History	The patient had a two week history of cough and the physiotherapist was asked to help with secretions
Other comments	Breathing became worse, HBr was added to the record of the effect.

Case profile C017	An 83 year-old female with carcinoma o
Relevant Past Medical History	The patient had a history of atrial fibrilla failure which had been controlled with tr
Other Comments	One litre of subcutaneous fluid was adr unusual practice at Hospice 1. The pati medical records to possibly have aspira difficulty clearing secretions. Consent w daughter gave an interview.

Case profile C018	A 76 year-old patient with carcinoma of carcinoma of the breast
Relevant Past Medical History	None noted
Other Comments	The patient was consented too late to k analysis. A percutaneous gastrostomy t analgesia was administered via a fentar medical records indicated that she was was administered via a syringe driver w 2.4mg in over 24 hours. This was contir injections being given. Medical staff rec it 'was effective', however nursing notes being most effective removing 'thick ten

Case profile SM122	Male patient 65 year- old with adenocar
Relevant Past Medical History	None noted
Other Comments	Consent was given for participating in th daughter became concerned at the regi in the patients care. Notes in the medic 'Dad would hate all this messing' Three 40mg were given over the last 48 hours

Case profile SM123	A male patient. 63years- old with metastatic adenocarcinoma of the pancreas.
Relevant Past Medical History	None noted
Other Comments	HBBr 120mg was administered via a syringe drive and a bolus dose of 40mg HBBr was given. There was no indication of why monitoring was not done. Nursing notes in the medical records only indicate that bolus HBBr was effective when patient became chesty.

Case profile SM124	A male patient, 69 years-old with carcinoma of the lung.
Relevant Past Medical History	Oxygen was given continuously. Nebulised ipratropium and salbutamol had been prescribed before the terminal phase.
Other Comments	Although the patient was consented monitoring was not carried out as the data collection form indicated of the patient that 'he was not chesty' HBBr was administered via the syringe driver for four days, starting at 80mg over 24 hours on the first day and at 120mg subsequently.

Case profile SM125	A 63 year-old male patient with non small cell lung cancer
Relevant Past Medical History	Continuous oxygen therapy was administered. Salbutamol was administered for wheeze.
Other Comments	One bolus dose of HBBr was administered. No reason was given for not monitoring After the notes regarding consent in the medical records, doctors recorded that the patient was not bubbly. At no time in the nursing notes was the patient noted to be bubbly

Case profile SM126	A 73 year-old female patient with metastatic carcinoma of the tongue.
Relevant Past Medical History	None noted
Other Comments	No mention of why this patient was not monitored. Nursing notes in the patients medical records indicated that HBBr 20mg bolus was given 'as secretions noisy and distressing to patient'.

Case profile SM127	A 76 year-old female with metastatic breast cancer.
Relevant Past Medical History	The patient required continuous oxygen. The patient's breathing pattern changed and became 'slightly bubbly', increasingly chesty and cyanosed
Other Comments	HBBr added to syringe driver. Oropharyngeal suction was performed and tolerated well. Thick green sputum was removed. During the night large amounts of thick creamy fluid was removed from the back of the mouth. Lack of monitoring of this patient may have been due to conflicting advice from nursing staff on duty at that time. Chest was commented to be 'very bubbly' With little response to HBBr which was added to syringe driver.

Case profile SM128	A 47 year-old male with Hodgkin's disease.
Relevant Past Medical History	The patients medical records indicated that the main problem was chest secretions
Other Comments	Three bolus doses of HBBr injection were administered. The patient was noted to be 'groaning and bubbly' and 'a bit chesty' after the last injection