

and communicating them. The former act, which has been the subject of this review, is a predicate for the latter, but we believe that both are necessary for patients to achieve a good death.

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Novel consent process for research in dying patients unable to give consent

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Abstract

Objectives To develop a process of advance consent to enable research to be undertaken in patients in the terminal phase.

Design Feasibility study of an advance consent process to support a randomised controlled trial of two antimuscarinic drugs (hyoscine hydrobromide and glycopyrronium bromide) in the management of noisy respirations associated with retained secretions ("death rattle").

Setting Palliative care wards in a major cancer centre.

Participants Patients admitted to a palliative care ward who may develop "death rattle" and thus be eligible for randomisation.

Main outcome measures Patient accrual; acceptability of the consent process.

Results Of the 107 patients approached to date, 58 patients gave advance consent to participate in the study. Of these, 15 patients developed death rattle and were randomised to receive either hyoscine or glycopyrronium; 16 patients died elsewhere; 15 patients died on the palliative care wards but were not randomised; 12 patients are still alive.

Conclusions Initial assessment suggests that this is a workable consent process allowing research to be undertaken in patients who are unable to give consent at the time of randomisation. Patient accrual rates to date are lower than needed to recruit adequate numbers in the time allotted to answer the research question.

Introduction

In order to participate in a clinical trial patients must receive, comprehend, and retain all the information necessary to allow them to give fully informed consent

for that trial.¹ Only fully informed consent can protect patients' autonomy.² Obtaining such consent is often very difficult in some disciplines, such as emergency medicine, elderly care, and palliative care.³⁻⁵

Dying patients are often unable to clear secretions from their large airways, resulting in noisy breathing usually described as "death rattle." This can be distressing to relatives and people caring for dying patients. Two antimuscarinic drugs are commonly used for the control of this condition. Hyoscine hydrobromide, a tertiary amine that can cross the blood-brain barrier causing central nervous system side effects, has historically been the drug of choice. Glycopyrronium bromide is a quaternary amine that does not cross the blood-brain barrier.

Our aim was to undertake a study to assess the relative efficacy of hyoscine and glycopyrronium in the control of death rattle within the context of a randomised controlled trial. To do this, we needed a means of obtaining consent from patients who would be unable to give consent at the time of randomisation. In the United Kingdom no established legal means exist to obtain consent in such situations.

After consultation with ethicists and lawyers, our local ethics committee advised us that the development of an advance consent process was the only possible means of obtaining consent in this situation. This paper details a method of obtaining advance consent and the interim results of the recruitment process.

Methods

All patients admitted to the palliative care wards in the Royal Marsden Hospital are given an information sheet explaining that they might be approached about research studies during their admission. The "trial suitability" of patients is determined at pre-round



The patient information sheet is on bmj.com

multidisciplinary meetings. Patients too unwell, unable to understand English, or likely to be distressed are not approached.

At the next ward round, the consultant tells all potentially eligible patients of the “noisy breathing” study and asks them if they would be prepared to enter the study if they were ever to develop difficulty breathing because of retained secretions. The consultant reassures patients that this is not a problem that they have at the moment but one that may develop in the future.

If patients are able to understand the preliminary information, are able to read the trial information, and express interest in the study, we give them the patient information sheet (see bmj.com). Relatives and carers are often involved in helping the patient to read and understand the leaflet. The research nurse asks patients if they understand the study, answers any questions or concerns, and ascertains if they are willing to enter the study.

We then ask patients to sign the consent form in the presence of one of the study investigators. The research nurse, ward nurse, or the patient’s relative or carer witnesses the consent. We reassure patients that they are free to change their mind at any stage and that refusal to enter the study will not prejudice their future care. Once consent is obtained, glycopyrronium bromide and hyoscine hydrobromide are prescribed on the “as required” section of the patient’s drug chart. The patient’s agreement to enter the study is documented in the medical and nursing notes.

At each subsequent admission, we ask patients if they are still prepared to enter the study. We ask them to re-sign the consent form on each occasion. The prescription for antimuscarinic drugs can then be rewritten. If the patient is unable to re-sign the consent form, we ask the patient’s relatives or carers if they know of any reason why the patient might have changed his or her mind about being in the study. If no indication exists that the patient had changed his or her mind, we consider the last consent to be valid and document it as such. If the patient subsequently develops noisy breathing needing treatment, he or she is randomised.

Our statistician advised us to do an interim analysis to determine whether the consent process was working and if adequate numbers of patients were likely to be accrued for us to be able to assess the relative efficacy of the two drugs.

Results

In the seven month period from May to November 2002 we considered 107 patients for entry into the study (figure). Of these, 34 declined and 15 subsequently proved unable to consent. Fifty eight patients gave informed consent and were entered into the study. By January 2003, 15 of these patients had died on the palliative care wards but had not been randomised, because they did not develop death rattle, they died suddenly, or they were missed from the randomisation process. Sixteen patients died at home or in other units. Twelve patients are still alive. Five patients have re-consented once, and two patients have re-consented twice. We randomised 15 patients to

receive either hyoscine or glycopyrronium at the time of death. We have not yet analysed the effectiveness or otherwise of the two agents in the patients recruited to date.

Discussion

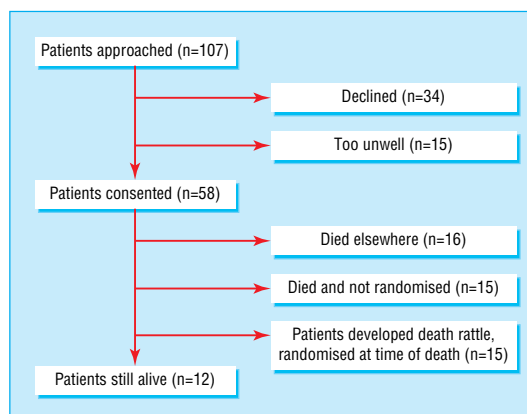
We have previously considered the factors that influence participation of patients in clinical trials in palliative care.⁶ We developed this consent process in an attempt to improve recruitment of patients to trials in palliative care.

Assuming that the true rate of control of retained secretions at the time of death with both agents is about 60%, we would need to recruit 250 patients to support the hypothesis that glycopyrronium is as effective as hyoscine in the management of death rattle. Approximately 200 patients die in the two palliative care wards at this hospital each year. We estimated that about half of these patients would develop death rattle. Therefore, we might hope to randomise 75-100 patients a year and to complete the study in three years.

Of the 58 patients who gave consent in a seven month period, we subsequently randomised 15. Twelve patients have given consent and may be randomised in the future. Although the “process” is working well, we are unlikely to achieve our recruitment target without the participation of local hospices or other palliative care centres. Initial estimates of recruitment were over-optimistic. Many patients are too unwell even on their first admission to receive the information needed to give consent. More patients than expected were never readmitted to the unit and therefore never randomised despite having given consent.

Slight concern remains as to whether the patients consenting for this trial can ever be fully informed. Even if they have witnessed other patients with death rattle, they may not equate this with the condition being studied. Similarly, they may read the information less carefully if they consider the trial to be a distant event that may never happen. The ethics of “advance consent” for research in emergency medicine have been questioned.⁷

Very few patients have been distressed when approached about the study. The relatively high refusal rate indicates that patients feel free to decline entry if they are not willing to participate. The follow up visit



Patient flow in the study

What is already known on the topic

Research to improve the evidence base behind the management of dying patients is very difficult

Patients in the terminal phase are given a large number of different drugs and subjected to many interventions of unproved benefit

Dying patients are usually too unwell to give informed consent for trials

What this study adds

This study presents a consent process that allows patients to consent in advance to a trial for which they may be eligible at a later date

If accepted, this process has the potential to facilitate research in the care of dying patients

randomisation and assessment process would make the current study very difficult to undertake by palliative care teams caring for patients in their own homes.

Research in palliative care is notoriously difficult.⁸ If generally accepted, this consent process may provide a means of increasing the number of patients in the terminal phase entering trials. This is essential if we are to improve the evidence base underpinning the practice of palliative care and improve the care of dying patients.

We thank the nursing and junior medical staff on Horder and Chevallier Wards at the Royal Marsden Hospital; J Riley and K Broadley for recruiting and consenting patients; research nurses B Gwilliam and A Kennett; Roger A'Hern for statistical advice; and the ethics committee of the Royal Marsden Hospital.

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by the research nurse after the consultant ward round allows patients the opportunity to decline entry in those cases where an initial acceptance might have been made only to "keep the doctor happy." Our records show that patients are much more likely to agree to enter a study when asked by a doctor than by a nurse.

Despite the fact that accrual has proved slower than anticipated, we believe that this is a workable means of obtaining consent for trials in terminally ill patients who cannot give consent. Our accrual figures to date indicate that we must involve other centres in order to recruit the patient numbers necessary to answer the research question. The complexity of the

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Fear of imminent death

Edgar Allen Poe (1809-49) shifted the boundaries of fiction in the genres of detective stories, science fiction, and tales of horror. Death—especially fear of it—is a recurring theme in Poe's work. This fascination may result from Poe's own losses: his parents died before he was 3 years old. Poe married his 13 year old cousin, Virginia, in 1836; she died at the age of 24.

Poe wrote *The Masque of the Red Death* while Virginia was sick with tuberculosis. Perhaps the blood she coughed up inspired Poe's fictional plague—the red death was "so fatal ... so hideous ... the madness and the horror of blood ... sharp pains, and sudden dizziness, and then profuse bleeding at the pores ... the whole seizure, progress, and termination of the disease were incidents of half an hour." The protagonist, Prospero, holds a masquerade to forget the suffering beyond his walls and forbids his guests to wear red. But one guest defies him. "And now was acknowledged the presence of the Red Death ... And one by one dropped the revellers in the blood-bedewed halls of their revel, and died each in the despairing posture of his fall." The story parallels Virginia's struggle against death and her final inability to escape: "And darkness and decay and the red death held illimitable dominion over all!"

Ironically, Poe's death was as mysterious and controversial as his stories and his life. Poe was found dishevelled in Baltimore—he was living in New York—and was taken unconscious to hospital. He lapsed in and out of consciousness for several days, until, with the words, "Lord help my poor soul," Poe died aged 40. The events that led up to his tragic and miserable death will never be known.

Richard Hurley *technical editor, BMJ*

www.poemuseum.org celebrates Poe's life and includes *The Masque of the Red Death*—one of his most famous short stories.

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.