TITLE

Collecting biological material from palliative care patients in the last weeks of life: a feasibility study

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ABSTRACT

**Objective**

To assess the feasibility of prospectively collecting biological samples (urine) from palliative care patients in the last weeks of life.

**Setting**

A 30 bedded Specialist Hospice in the North West of England**.**

**Participants**

Participants were adults with a diagnosis of advanced disease able to provide written informed consent.

**Method**

Potential participants were identified by a senior clinician over a 12 week period in 2014. They were then approached by a researcher and invited to participate according to a developed recruitment protocol.

**Outcomes.**

Feasibility targets included a recruitment rate of 50%, with successful collection of samples from 80% who consented.

**Results**

A total of 58 patients were approached and 33 consented (57% recruitment rate). Twenty five patients (43%) were unable to participate or declined; 10 (17%) became unwell, too fatigued, lost capacity, died or were discharged home; 15 (26%) refused, usually these patients had distressing pain, low mood or profound fatigue. From the 33 recruited, 20 participants provided 128 separate urine samples; 12 participants did not meet the inclusion criteria at the time of consent; 1 participant was unable to provide a sample. The criterion for a urinary catheter was removed for the latter 6 weeks. The collection rate during the first 6 weeks was 29% and 93% for the latter 6 weeks. Seven people died while the study was ongoing, and another 4 participants died in the following 4 weeks.

**Conclusion**

It is possible to recruit and collect multiple biological samples over time from palliative care patients in the last weeks and days of life even if they have lost capacity. Research into the biological changes at the end of life could develop a greater understanding of the biology of the dying process. This may lead to improved prognostication and care of patients towards the end of life.

**ARTICLE SUMMARY**

**Strengths and limitations of this study**

* This is the first investigation to prospectively collect biological samples from patients towards the end of life and in the dying phase.
* The study raises the possibility of conducting systemic research into the biological changes in patients towards the end of life.
* All of the participants who subsequently died on the study had a cancer diagnosis. It therefore does not accurately reflect the dying process patients with a non-cancer diagnosis go through.
* Our findings are consistent with other studies that confirm patients in a hospice are keen to be involved in research.
* The study was found to be acceptable to patients, their families and the staff; however, there was no formal process used to assess this.
* The protocol described can be used in future research.

INTRODUCTION

Clinicians find it difficult to diagnose accurately when someone is dying. There is no evidence based method of consistently and accurately estimating an advanced cancer patient’s prognosis. Existing methods of predicting prognosis are no more accurate than a multi-professional prognostic estimate1. Uncertainty has been recognised by health-care professionals as a great barrier to the provision of good palliative care2. This prognostic uncertainty may lead to a lack of appropriate intervention or prompt inappropriate and burdensome interventions. Accurate prognostication is crucial for patients, their families, the treating medical teams and health care providers to plan and provide the best possible care for patients at the end of life.

Understanding of the biological process of dying is limited. The current evidence base informing terminal care is largely descriptive, retrospective or extrapolated and there are no empirical studies investigating biochemical changes during the dying process3. A review of end of life care in the UK and the National Care of the Dying audit in hospitals conducted in England both recommended research into the recognition of dying4 5. The collection of biological samples would allow for the use of systemic research methods including molecular and metabolomic approaches to investigate the dying process.

Conducting research to understand the biological processes at the end of life is difficult due to the numerous logistical, practical and ethical challenges of collecting data at this time. Obstacles to research include: the heterogeneous nature of the patient population due to variants in primary disease and both concomitant and independent co-morbidities; the high prevalence of cognitive problems which impact upon capacity; the unstable nature of the disease process; the lack of research infrastructure and experience in palliative care teams; ‘gatekeeping’ (i.e. preventing access to potential research subjects by clinical staff)6. However, research is essential to improve patient care and for palliative care to develop as an evidence based specialty7.

In this paper we evaluated the feasibility of collecting multiple biological samples (urine) from hospice patients in the last weeks and days of life, including patients who lost the capacity to give consent.

METHODS.

Setting and Participants

The study was conducted at a 30-bedded Specialist Hospice in the North West of England over a 12 week period during 2014. The hospice provides care for patients with life limiting diseases with both cancer and non-cancer diagnoses. Ethical approval was provided by North Wales (West) Research Ethics Committee (REC reference 13/WA/0266). Participants were enrolled in the study provided they met eligibility criteria (Table 1) and informed consent was provided.

**Table 1 – Study Inclusion Criteria**

|  |  |
| --- | --- |
| Inclusion Criteria | Exclusion Criteria |
| * Inpatient at the Hospice
* ≥18 years of age
* Patient able to understand and communicate in English
* Urinary Catheter in situ (weeks 1-6 of study only)\*
 | * Patient unable to provide fully informed consent
* Judgment made by senior doctor on the clinical team that approaching patient about the study would cause undue distress
* Patients too unwell. (This was a clinical decision made by the treating team)
* Patient unable to understand English
 |

\* During the first six weeks of the study, a urinary catheter was part of the inclusion criteria. With an amendment to the research ethics approval, this requirement was withdrawn for the latter six weeks of the study to facilitate increased participation.

**Enrolment procedure**

The research method, including participant selection, was designed to minimise the potential for distress caused by recruiting in this challenging and emotive phase of life. There was extensive discussion amongst the team and consultation with a patient advisory group about the title on the documents used - ‘Investigation of the biological changes in urine towards the end of life – a feasibility study’. All existing and new inpatients at the Hospice were considered potential participants. A senior doctor (Registrar or Consultant) on the clinical team reviewed each inpatient to evaluate whether an approach about participation in the study would cause distress. If deemed appropriate, the patient was provided with a one page introductory Patient Information Leaflet and permission for a research team member to approach was requested. Prior to the study commencing, education sessions were held with the hospice staff to outline the purpose of the study and what would be involved. A research team member then approached the potential participant and discussed a detailed three page Patient Information Leaflet, which explained the purpose of the study as follows: “we plan to analyse the urine of patients with advanced disease and how this changes towards the end of life. There is very little known about changes in a person’s body at this incredibly important time. By doing this study we want to examine if the physical experiences of the patient can be seen in the genes and in the chemicals found in urine.”The patient was encouraged to involve their family in their decision making and was given appropriate time (minimum 24 hours) to consider their participation and have the opportunity for further discussion with their family, friends, hospice clinical staff or research team. The patient’s agreement to enter the study was documented and the signed consent form was placed in the medical notes; a copy was also given to the patient and an additional copy kept for the research site file. Medical records and medication charts were reviewed to collect the age, race, diagnosis and, if appropriate, known metastases, co-morbidities, medications, smoking status and catheter system used. Some participants were asked to clarify demographic questions. Once informed consent was obtained and all inclusion criteria were met, sample collection began. Participating patients who were discharged from the hospice and subsequently re-admitted were asked to re-confirm their consent to participate verbally. The process for enrolment is outlined in Figure 1.

**Figure 1 Process for enrolment**

**Sample Collection**

Since potential participants could lose the ability to provide consent as the study progressed, participants were asked specifically whether they agreed to continue with sample collection should they lose the ability to consent. Prior to sample collection, the capacity of the participant was assessed for ongoing assent to collect samples. If a participating patient’s clinical condition deteriorated to the extent that the patient lost capacity to consent to sample collection, then a Consultee was identified to advise the researcher about the participant’s ongoing continuation in the study. The Consultee was selected as per ‘Guidance on nominating a consultee for research involving adults who lack capacity to consent’ (Department of Health, UK). Initially, a Personal Consultee was consulted for advice. They were ideally someone who knew the participant well but were not acting in a professional or paid capacity e.g. next of kin, immediate family, relatives or friends. If a Personal Consultee was not identified or unable to attend the hospice then the researcher nominated a healthcare professional (a hospice doctor or nurse who was involved in the patient’s care), unconnected with the research who was willing to act as a Nominated Consultee. The Nominated Consultee then contacted a family member and listened to their views if it was the first time that the participant was unable to give consent. The ‘Consultee’ was given a ‘Consultee Information Leaflet’ and given time to consider it. If after reading this they were in agreement with the participant continuing in the study, they were asked to sign a ‘Consultee Declaration Form’. Only then was a sample collected. If the participant continued to lack capacity, then permission to collect urine was sought from the Personal (or Nominated) Consultee each time a sample was collected.

Withdrawal of Subjects

Patients were informed both verbally and with the Patient Information Leaflet that they could withdraw from the study at any time and no reason for withdrawal was required. It was emphasised that their clinical care would not be affected. If a participant withdrew from the study or the Consultee requested withdrawal, no reason was required. However when they shared their reason with the research team or a member of the Health Care Staff, this was recorded in the study database.

**Sample Collection**

Biological samples were collected three times a week by the research team. Research team members collected 20mls of urine from participants in a universal container. For those participants with a urinary catheter, the urine was collected using a needle and syringe from the catheter port. The samples were stored on site in a locked freezer at -20C. An anonymised record of the medication administered was collected.

Feasibility Criteria

We designed a priori criteria which included the following conditions: recruitment rate of at least 50% and the collection of urine samples from 80% of those who consented. There are no established precedents for what constitutes successful recruitment within a feasibility study of this type. However, we have engaged the outcomes from the Prognosis in Palliative care Study (PiPS), which is the closest in terms of focus to set the bar for recruitment. The PiPS study recruited 43% within a hospice setting and we decided to target 50%1. Hagen et al state palliative care studies can have attrition rates of 50% or higher8. Despite this we aimed for a collection rate of 80%.

Statistical Analysis

The primary reason for this study was to establish feasibility of collecting biological samples from patients in the last weeks of life. The target sample size was n=20, which was determined primarily based on feasibility considerations to test procedures for a larger study. The sociodemographic and outcome variables are reported using descriptive measures including the mean for continuous variables and number (percent) for categorical variables. The analysis of feasibility outcomes was descriptive in nature, with the results expressed as percentages and feasibility assessed against the corresponding targets.

RESULTS

In total 128 separate samples from 20 different participants were collected (see Table 2). Four participants lost capacity while on the study and the Consultee Declaration Form worked well in facilitating the continued sample collection for these participants.

56% (n=58) of inpatients at the hospice were approached. Of the patients who were not approached 53% did not have capacity (e.g. dementia, brain primary or secondary, delirium); 16% were actively dying; 13% had too short an admission; 17% were deemed inappropriate to approach (anxiety 13%, anger 2%, low mood 2%).

From the 58 patients approached, 33 consented to participate in the study (57%). No problems were identified with the information leaflets and consent form used. Only one patient asked a researcher to leave during the discussion of the patient information leaflet**.**

The protocol used was found to be acceptable to participants, their families and staff and no episodes of distress were encountered. This was not formally assessed; however, no complaints were received regarding the discussion of the study protocol in recruitment, or the collection of study data and only one patient asked a researcher to leave during the discussion of the patient information leaflet. One participant withdrew from the study (5%). One patient who consented and discharged was readmitted and reconsented during the study.

Of the 43% who did not consent, 40% of those approached became unwell, too fatigued, lost capacity, died or were discharged home. The remaining 60% refused; usually these patients had distressing pain, low mood or profound fatigue. This is summarised in Figure 2.

Within the first six weeks of the study, 17 patients consented to participate. As a urinary catheter was part of the study inclusion criteria only five of these participants were eligible to have samples collected (collection rate of 29%). Due to the high consent rate and low collection rate early in the study, an amendment to the Research Ethics Committee was made to remove having the urinary catheter as part of the inclusion criteria. During the latter six weeks, following the approved amendment to the protocol, 15 participants were recruited (collection rate of 93%). Samples were not collected from one patient despite multiple attempts over a two week period. One patient asked to withdraw from the study after the collection of one urine sample as it was felt ongoing collection was considered too burdensome. Seven people died while the study was ongoing and another 4 participants died in the following 4 weeks.

**Figure 2 A summary of the patients approached and consented during the study**



Table 2 Summary of participant details and samples collected

|  |  |
| --- | --- |
| **Age (years)**RangeMeanMedian | 50-9070.667.5 |
| **Sex**MaleFemale | 911 |
| **Diagnosis (Number of cases)**Cancer- Lung - Breast - Colorectal - Prostate - Ovarian - Gastric - RenalNon-Malignant- Multi-System Atrophy - Motor Neuron Disease | 633311111 |
| **Number of samples collected**RangeMeanMedian | 1-1865 |
| **Number of samples collected in the weeks before dying**Week 1Week 2Week 3Week 4 | 15 samples from 6 participants17 samples from 9 participants21 samples from 8 participants10 samples from 6 participants |
| **Participants in the last 4 weeks of life** | 11 |
| **Participants alive more than 3 months after the study** | 6 |

DISCUSSION

Research into the physiology of the dying process is difficult. This paper describes a protocol for the collection of biological samples (urine) from hospice patients towards the end of life and during the dying process. There was a 57% recruitment rate of inpatients, and a collection rate of 93% when urine was collected from participants with or without a urinary catheter. A total of 128 separate samples from 20 different participants were collected over the 12 week period.

The study confirms the ability to prospectively recruit patients and collect multiple urine samples towards the end of life and in the dying phase, including when a person has lost the capacity to give consent. The protocol used was found to be acceptable although this was not formally assessed. One participant withdrew from the study (5%). Attrition rates of 50% and even higher have been described in other palliative care studies8. The methodology used benefited greatly from the input of the patient representative group and by asking the medical team to screen patients before a researcher approached. Four participants lost capacity while on the study and the Consultee Declaration Form worked well in order to continue sample collection. The involvement of family through the consent process and sample collection helped in ongoing sample collection in those participants when mental capacity was lost. In fact, some patients and families derived meaning from being able to contribute to the study.

During the study the requirement for a urinary catheter as a criterion for sample collection was removed after six weeks. This was due to the low recruitment rate (29%) when samples were collected from 5 out of 17 patients who had consented to the study. The change facilitated an increased recruitment rate (93%).

**Challenges within the study**

Challenges to sample collection included the necessity for sensitive communication skills, the timing of sample collection, patients who were unable to sign the consent form and patient fatigue. During the consenting process, finding the appropriate words to describe the rationale for the study required experience and training in advanced communication skills; both researchers were experienced palliative medicine physicians. Urine collection from participants who did not have a urinary catheter highlighted issues to be considered in future studies. Participants had variable mobility and providing a urine sample could be inconvenient for them if they were not otherwise going to the toilet. One patient who consented to the study was unable to provide a sample despite 6 attempts over a 2 week period. Another patient was able to provide only 1 sample over the same time period. There were some participants who could initially provide samples but over time as their disease progressed and their mobility decreased, samples became more difficult to collect which caused gaps in sample collection. There were also times when it was challenging to engage with the medical teams, for example on ward round days. This sometimes caused a delay in the clinical team approaching a patient for initial consent. Other challenges included 2 participants who were unable to write their signature on the consent form; and those patients with severe fatigue who often felt unable either for the entire initial discussion or the subsequent follow-up meeting to consent to the study. Therefore, it would be important in any future work to keep the patient information leaflets and consent forms as short as possible.

The majority of participants recruited had a cancer diagnosis (90%) and all of the samples collected in participants who subsequently died had a cancer diagnosis. As a result this cohort does not represent the dying process of people with a non-malignant diagnosis. Also, all of the participants recruited were of a white British background and were therefore not a broad cultural cross-section of patients.

 Palliative patients can have a variable prognoses ranging from years to days or hours. Those patients towards the end of life (in the last weeks of life) are an important and understudied patient population. It is imperative that no distress is caused to them or their families and this is a concern to all parties involved in research. However, our protocol addresses these important concerns. In the hospice we discussed with the treating team the appropriateness of patients being included in the study, for example whether the patient was aware of the advanced nature of their disease. This could be considered a form of gatekeeping.

**Challenges for future research**

This study highlights a cohort of patients who on admission to a hospice had already lost capacity and therefore could not take part in the study. In particular, this included patients with dementia, brain tumours and those actively dying. In the UK the Mental Capacity Act of 2005 prevents the recruitment of patients to research studies who are unable to give consent. A future challenge in the UK will be to design studies to include this cohort of patients.

Prior studies do suggest that palliative patients want to participate in research9 10 and our study confirms this. The consent rate of 57% of those approached was encouraging and affirmed the importance of conducting research into end of life care for these patients and their families. The Prognosis in Palliative care Study (PiPS) which recruited palliative patients from 18 palliative services in the UK had a 43% recruitment in the hospice setting, demonstrating that access to palliative patients was significantly easier in the hospice as compared to other settings6. The PiPS study and the Rees and Hardy study, which developed a process of advance consent to enable research to be undertaken in patients in the terminal phase, reported that very few patients were distressed when approached. Rees and Hardy also reported that the consent process can be very time consuming and emotionally draining for staff11.

Stone et al reported that obstacles to research include the nature of the patient population, the high prevalence of cognitive problems, the unstable nature of the disease process, the lack of research infrastructure and experience in palliative care teams and ‘gatekeeping’ (i.e. preventing access to potential research subjects by clinical staff)6. Stone et al also mention common reasons for inaccessibility of patients; died before review, gatekeeping, discharged before review, patients did not wish to see a researcher, non-competent patient and relatives unavailable, researcher unavailable, patient unavailable. Our own study reflected similar challenges, although we did not find gatekeeping to be an issue.

As reported by Rees and Hardy, patients on palliative care wards often have a poor performance status and are too unwell to read lengthy patient information sheets11. They are therefore unable to give consent. In addition, patients are often reported to be too anxious to understand complex study descriptions12. Therefore, from our experience and the experience of other studies it is important in any future work to keep the patient information leaflets and consent forms as simple and as short as possible6 13.

 Diagnosing when a patient with advanced cancer is in the last weeks or days of life is a challenge; currently no diagnostic test is available5. Accurate prognostic information is essential to co-ordinate and manage care in response to need, whilst avoiding burdensome and unnecessary interventions. Even though little is known about the biology of dying, it has been suggested that that there may be a common process to dying14 15. Future work will involve systemic research approaches including metabolomic and genomic analyses of the urine samples. The aim of this research would be to develop a greater understanding of the biological process of dying and identify potential biomarkers for the dying process.

**CONCLUSION**

This paper describes a study for the collection of biological samples from patients towards the end of life including those without capacity. Importantly, the protocol used minimises undue distress to patients or their families. By incorporating the consultee process, the protocol overcomes the legal and ethical requirements in patients who lose mental capacity. It is our hope that this protocol will aid others to collect samples from what is considered to be a difficult cohort of patients to study. Research into the biological changes at the end of life could develop a greater understanding of the dying process. This may lead to improved prognostication and care of patients towards the end of life.

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**Authors Contributions**

All authors were involved in critical review of the manuscript and have seen and approved the final version. Specific contributions as follows; Study conception and design: SC, RL, SM, CM, AN, JW, CP JE; Sample acquisition: SC and AS; Drafting the manuscript: SC, AS and SM; Revision of manuscript: AN, RL, CM, JW, CP, JE.

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**Competing Interests**

None

**Data sharing statement**

No additional data available

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