
THE UNIVERSITY *of* EDINBURGH

# Resource use and costs at the end of life

## Essays on common ways to collect data on resource use and derive costs at the end of life in a UK setting

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Dissertation for the Degree of Doctor of Philosophy,
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*I am dedicating this thesis to two beloved people who have meant and continue to mean so much to me.*

*First and foremost, to my grandmother Gerlinde whose love and understanding for all of her children, grandchildren and great- grandchildren knew no bounds. I loved being at yours as a child and even more so as an adult; I enjoyed our daily coffee break whenever I was back home and our countless video-calls when I was abroad. Your unique, open and none judgemental mindset in connection with your witty humour and directness made you the most amazing person to be around. I feel honored that I was able to spent so much time with you and that you allowed me to accompany you in your last hours. I love you!*

*The second person is my godmother Eva. You were my inspiration to push towards a higher education, to challenge opinions, to explore more of the world and to work and fight hard for what you think you deserve. You taught me to never blindly accept boundaries set by others and that it needs a lot of courage to find your own way. Thank you Eva for your guidance, chat and banter, the countless emails and phone calls, the visits ... and for being an amazing friend!*

*I would have loved for the both of you to sit in the first row at my graduation.*

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Thank you!

Danke!

*Edinburgh, August, 2022*
*Katharina Diernberger*

# Declaration

I wish to submit the thesis detailed above in accordance with the University of Edinburgh research degree regulations. I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Where appropriate I have acknowledged the nature and extent of work carried out in collaboration with others.

Parts of this work have been published. Publication type, collaborators and the journals are specified within the thesis.

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# Abstract

**Background:** Within the given environment of limited health care resources and increasing demands on the health care system, it is imperative to organise health care in the most efficient manner. Sustainability of the overall system, equity issues concerning access to care and a move to patient-centered care - informing the decision making process by patient needs, are current hot topics when considering patients' end of life or curative care.
The decision making process within UK's health care sector relies on a standardised approach including the benefits and the costs of interventions and "guarantees" that resources are used in a way which provide best value. This approach falls short when looking at interventions tailored to the end of life, jeopardising appropriate attention for end of life and palliative care.

**Aim:** The aim of the thesis is threefold:

1. Understand the current landscape of 'resource use data collection' and deriving costs at the end of life in an UK setting.

2. Reflect on the challenges, benefits and limitations of using administrative data versus trial data in an end of life care setting.

3. Present potential solutions to challenges arising from collecting and analysing cost of end of life care and recommendations for further research.

**Methods:** This work starts by highlighting why end of life care is an outlier when considering the measurement and allocation of health care resources. Then an update of a systematic review is included to identify currently used approaches to capture resources used and cost assignment at the end of life. Further chapters discuss administrative data use and data gathered within clinical trials, highlighting benefits and limitations of administrative data studies and two clinical trials, both of which are underpinned with two case studies.

The administrative data studies are retrospective, whole-population, secondary care administrative data linkage studies, capturing resources used in the last year prior to death.

The first clinical trial is a two-arm parallel group cluster randomised (1:1) trial on pain assessment; the second, a feasibility trial of an Exercise and Nutrition-based Rehabilitation program at the end of life.

**Results:** The results from the included studies are in line with the results from the systematic review. There is no clear structure in resource use collection and the derivation of costs in end of life care within the UK, not even on a smaller scale when looking at Scotland only.

Costing based on routinely collected data, as well as costing based on data collected within trials, comes with specific benefits and limitations, some of which could potentially be addressed when combining data generated through trials with administrative data.

**Conclusion:** Fair, evidence based decision making requires comprehensive knowledge of the current state of the system, being conscious of the costs and the benefits of interventions and having a system in place which enables comparison of different interventions, which in itself requires a standardised way to capture costs and

benefits.

This thesis presents various examples of different approaches to resource use collection and applying costs. In order to be able to recommend at least a Scotland wide costing strategy for costing administrative datasets, more research is needed to understand the impact of applying different costing methods to the same dataset. Within clinical trials, collection of resource use data should be kept to the minimum in order to keep patient burden low. The development of a standardized questionnaire is recommended, highlighting the need for adaptability to different trials.

Linkage between data collected from individual trials and administrative data is an appealing concept, offering extensive data whilst keeping the patient burden at a minimum. Looking at the current landscape of data protection regulations, there are yet some hurdles to overcome.

# Lay Summary

Most people experience ill health when they are near to the end of life and may often need a lot of healthcare at this time. Caring for patients at the end of life can be costly for the health care system.

Resources in the healthcare system are limited. We need to know how, when and where they are used to be able to make sure that we help patients as much as possible. This can also be thought of as getting the best value for money for spending on health care. Little is known about what resources are really used in end of life care currently, or how much cost is needed to provide the highest standard end of life care.

One of the reasons that little is currently known about this topic is that understanding the cost of care at the end of life can be difficult. There are various ways to try to accurately measure resource use. These range from just looking at the costs within one part of the health care system, to looking at the costs to the whole society. Another difficulty is that records of care at the end of life are complicated. There are many sources of records, various different prices that are used, and different ways of adding them up. We need to try a range of different ways of using the available records so that we can avoid mistakes such as missing some cost or counting some costs twice.

This work compares some of the ways of measuring resources used in research. The goal of this work is to get a better understanding of the current landscape of information collection and how costs are reported in the UK. Additionally, the benefits and limitations of the different ways of measuring resource use at the end of life are explored.

The first part of this work includes a review of the literature to make sure how costs are currently measured in end of life care studies is understood. This is followed by two studies which looked at measuring resource use at the end of life using administrative data (information which is automatically collected whenever you have contact with the health care system).
The third part includes two studies that measure resource use at the end of life within clinical trials. Clinical trials are highly controlled research studies of new treatments and processes in healthcare. This work shows the data collection and costs connected to those projects.

The first study using administrative data estimated the cost of the last year of life (hospital based care only) at £10,134 per person. It included all different kind of diseases. The second study, which looked at cancer patients only, showed a higher average cost of £12,513 for the last year of life. Further, both studies showed a lot of differences between they type of illness in the first and the type of cancer in the latter. A lot of the difference in cost was down to the age at which patients died, with older patients using considerably less hospital-based health care.
The first clinical trial included, looked at a structured way to capture and treat pain and looked at pain-related costs only. Within the study population, pain was treated better, faster and at a lower cost than if a more standardised approach was used. The second study was a small trial looking at exercise and nutrition based interven-

tion at people's end of life. It captured a wide variety of costs, hospital-based care, community care, charities and costs for the patients themselves and their family. It showed that an intervention is beneficial to patients' health and is likely to be cost saving.

Based on the experiences from the included studies there are several recommendations: first, a future study should compare different ways of adding up resource use using the same dataset. This should be set up so that it can more directly compare the different methods. Based on this we should be able to reach an agreement on the best method to use, both for administrative data and for trial data. This would overcome one of the problems ie of different studies not be comparable.

Another idea for future research is to use administrative data and data collected in trials at the same time, as this will help to reduce the burden on patients. Additionally this could add a lot more information to trials. Although this sounds easy, it might take a bit longer to work around all the challenges regarding data regulations.

Ultimately, making studies more informative by adding different data sources and increasing studies comparability, will help us to get an accurate understanding of the resources needed for high standard end of life care. The healthcare system can then use this information to ensure good value for money for the end of life care that is provided.

# Contents

# Imagine

*Patient A, a young professional lived in his first own home, away from family. He moved to the city to study and subsequently stayed. He had a reliable circle of friends and some work colleagues he kept seeing for after work activities. After having severe abdominal pain and generally not feeling well for several weeks (some days he had been fit enough to attend work, others not) he went to the GP who referred him to hospital, where he had undergone several scans and biopsies and was quickly diagnosed with stage 4 colon cancer. Due to his young age, life-prolonging treatment options were considered but it became obvious that he was too frail to tolerate chemotherapy after an unscheduled admission following the first chemotherapy dose, and needed to be switched to best supportive care. In addition, he had several symptoms which made it difficult for him to function: these included pain, nausea, weight loss and fatigue. The hospital nurses put him in touch with a patient support group run by a national charity, which also provided practical support with financial and work issues. His GP referred him to community palliative care for urgent symptom management and for discussion of social care needs. With the support of social care, the charity, community palliative care and his network of friends, the patient was able to stay at home for the first few weeks after diagnosis. Due to rapidly declining health and family being to far away and unable to care for the patient, he was soon admitted to a hospice.*

*Patient B, an elderly person who was living with her elderly partner in a rural community. She had been suffering from dementia for several years with a rapidly declining cognitive and physical function over her last months. Although her partner and children were putting a lot of effort into the patients care (helped with food shopping, assisting with tasks around the house and garden) the family relied heavily on community care. Due to her increased frailty the house needed some adaptations (stair-lift, walk in shower, hand rails...). Patient care used up a considerable amount*

*of time, as the patient couldn't be left on her own. Further, the family ran all errands and transported the patient to doctors and care appointments. In the final phase the patient's children took turns in taking time off work. When the family started being overwhelmed and the patient's condition dramatically worsened, a care home was organised. It was a very difficult decision for the partner and family and involved numerous visits to possible care homes. Shortly before she was moved the patient died.*

*Patient C, was suffering from a chronic heart condition and had several unscheduled hospital admissions over the last months. The disease was coming in waves with very bad spells at times and stable phases afterwards. The patients GP attempted to make contact during periods at home, but only managed to review the patient face to face once. He found it difficult to discuss the future and plan care as the family pointed out how well the patient was after each discharge. The community cardiac team were reviewing the patient at home and pointed out to family that an increase in hospital admissions was often associated with a worsening of the heart condition and that soon it may stop responding to treatment. The family had organised themselves to visit more often and were actively involved in organising more social care. One evening the patient suddenly deteriorated and was very distressed. The evening social care happened to be there. They immediately called their line manager who told to call 999 and ask for an ambulance. The patient attended A&E and was admitted to the High Dependency Unit where they died 3 days later.*

All of the above patient descriptions are "every day" examples developed with input from the palliative care team in Edinburgh. Looking at the above patients, it becomes obvious that broad and large variety of services are needed to assist patients and their family and friends in the final phase of life.

Care is delivered on several levels and in a variety of settings. Most of which are financed through different budgets, held in a variety of places. Crucial questions about intensity and quality of care arise, such as: What interventions are needed and are there any barriers in access e.g. equity issues, living too remote? What inter-

ventions are of value to a patient and their families? What are the most frequently used care pathways and are they aligned with patients needs and preferences? What costs are attached to the resources used and how much is covered by the health system? Which part of the health and social care system is liable for delivering and funding interventions. What is the best way of measuring quality of life and with that patient satisfaction and are there ways to improve the measurement?
Everyone familiar with end-of-life care will agree that care pathways are as diverse as the patients themselves. Research in the area of end-of-life care entails a frightening amount of open/unanswered questions, with seemingly endless opportunities.

This work will start with a holistic view including all care settings as well as patients quality of life but will narrow down on the cost side, trying to make a start with the seemingly "easiest" task of "just summing up" what real patients actually need(ed)!

Imagining the three patients and thinking about their "needs" in terms of resources used, it becomes evident that “costing” all patient needs at the end of life including formal palliative and end of life care has the potential to become very complex, especially when one aims to capture "ALL" costs.

Patients near their end of life are usually not just staying at one place but are moving between a variety of health services, whilst requiring different levels of care intensity during their journey.
A considerable share of costs is accumulated within the formal care sector as nearly all patients need some level of primary and/or secondary care in their final phase of life. Some patients might be placed in care homes or hospices which doesn’t allow us to preclude that they are moving between different settings. Informal care as well as formal community care and charities playing a major role in terms of

resource use and costs. A considerable share of care is dealt with within the communities and informal care. Community care in itself is multi-disciplinary, spread across places and includes several modes of contact such as phone, face-to-face and out-of-hours services. Further costs might be carried by the patients themselves, as home adaptions might be necessary, OTC medication needed and/or alternative medicine/treatments is/are bringing some relief.

What adds to the complexity is the fact that multiple of these services are frequented very prompt and yet we are just thinking about the patients and have not yet included costs for transportation, parking, additional laundry and many other possible services. Moreover are the costs accumulated at the end of life limited to the person dying? How to measure and cost the burden on the family, the wider social network, time missed or less productive at work (Absenteeism, Presenteeism), the societal cost?

# Chapter 1

## (In)compatible? Health Economics and End of Life Care

The following chapter aims to highlight the importance of conducting robust health economic analysis in an end of life care setting, whilst demonstrating some of the main challenges within the field. Parts of this introduction have been published in a more concise format as an Editorial titled "Incompatible: End of Life Care and Health Economics" (Diernberger, Shinkins, et al., 2021). The published version of the paper can be found in Appendix 6.A.1.

This chapter provides an overview of the topic, designed to be accessible to both health economic and clinical audiences and includes the cost and quality aspect of health care at the end of life. The focus of subsequent chapters will then be narrowed down to the costs associated with end of life care. This thesis used data from deceased people as well as trial data from terminally ill patient cohorts. The focus of neither of the included studies or trials was survival, rather data collection and/or analysis on the quality of life aspect and/or care pathways and there associated resources used.

## 1.1. (In)compatible?

*When it comes to death, the statistics are stark. 100 percent of us will die. The question is what are we all going to do about that? How are we going to create confidence in the care that we may need? (Palliative and of Life Care Partnership, 2015)*

During the last year of life, a significant proportion of healthcare resources are utilised. This includes money spent directly on interventions, but also the time of professional healthcare providers. Reflecting on this quote, it seems counter-intuitive that health economics could play a major role in tackling the main challenges in end of life care.

However, the escalating cost of healthcare, combined with an ever-increasing range

of therapeutic and patient management options and a growing population, has brought difficult budget allocation decisions to the fore. Palliative care services are now forced to seek transparent and evidence-based mechanisms for appropriate funding.

## 1.2. What is the value of health care?

A fundamental pre-requisite to distribute healthcare in an equitable way is the ability to measure both health outcomes and costs, in order that they can be counterbalanced.

*Brief digression:* The concepts of equity and equality are interrelated. Equality implies equal treatment for everyone independent from a potential difference in need; equity introduces some idea of fairness, that is treatment should be equal, when the need for that treatment is equal.

The concept of equity can be viewed through two lenses namely horizontal and vertical equity, with the first being defined as equal treatment for equal need (Abasolo et al., 2001; Morris, Sutton, et al., 2005). Vertical equity is complementary to horizontal equity; it is achieved when individuals with different need consume appropriately different amounts of care (Morris, Sutton, et al., 2005). Therefore in order to reach vertical equity utilisation of health care should be greater amongst those with greater needs (Abasolo et al., 2001).

The value of healthcare can be considered as what is gained relative to what is lost in terms of both, "costs" and "health". In our context, there are three value dimensions:

1. Population – how well assets are distributed to different sub-groups in society (equity in resource distribution).

2. Technical – how well resources are used for outcomes for all people in need in the population (improving quality and safety of services).

3. Personal – how well the outcome relates to the values of each individual (understanding what matters most to the patient).

Contrary to popular misconception, value is not the same as quality of care - or how much money is spent. High quality care to the wrong patient or at the wrong time (or in the wrong place), is still low value. Similarly, better value is not necessarily achieved by spending more money. Nevertheless, even to the right person at the right time, health care will still have an inevitable cost. Maximising value in healthcare resources requires understanding both what we seek to achieve and the effectiveness of the means to achieve it; this is the purpose of health economics.
People used to a universal health care system may struggle to understand that health care resources are limited and trade-offs are to be made, but rather perceive it as a basic right and rarely question where these resources originate. The idea that care could be rationed in a time of need seems alien.

## 1.3. What is health economics?

*"Economics is a science which studies human behaviour as a relationship between ends and scarce means which have alternative use" (Robbins, 1932).*
Thus, economics is a science of choice. Health economics is therefore the science of choice within the healthcare context. Countries typically set their healthcare budgets to a certain share of their overall gross domestic product (GDP). The aim is to distribute a constrained health budget to maximise overall population health.

A key concept of economic theory is 'opportunity cost', defined as *"(t)he value of*

*forgone benefit which could be obtained from a resource in its next best alternative use"* (Ferraro and Taylor, 2005).

Fundamentally, money spent on a certain intervention/treatment/drug cannot be spent on something else - even though that may also have had a beneficial outcome. In reality, health care systems are so complex that the opportunity cost is typically NOT identifiable i.e. we do not know what other health care intervention we may have displaced.

The economic evaluation framework quantifies the pros and cons of specific health interventions and balances them against the cost (which might be to the system or the individual). With such a framework, we can therefore reduce "waste" by identifying and exchanging interventions that may be of minimal benefit for more effective ones. Nevertheless, there are a lot of cost-effective interventions to choose from and it is getting more challenging to pick the "right" interventions.

## 1.4. Definition of end of life care and palliative care in this work

The General Medical Council (GMC) defines Palliative Care as: *"The holistic care of patients with advanced, progressive, incurable illness, focused on the management of a patient's pain and other distressing symptoms and the provision of psychological, social and spiritual support to patients and their family."* Palliative care is not dependent on diagnosis or prognosis, and can be provided at any stage of a patient's illness, not only in the last few days of life. The objective is to support patients to live as well as possible until they die and to die with dignity (GMC, 2019).

The definition provided by the European Association for Palliative Care (EAPC) adds the interdisciplinary nature and states palliative care *"encompasses the care of*

*the patient and their family".* In addition, the EAPC covers different locations including hospitals, hospices and community settings in which palliative care takes place.

EAPCs "white paper" states that End-of-life care is frequently used synonymously with palliative care or hospice care, whereby the 'End of Life' is understood as *"an extended period of one to two years during which the patient/family and health professionals become aware of the life-limiting nature of their illness" (Radbruch and Payne, 2009).*

The GMC defines people as 'approaching the end of life' as those who are likely to die within a time frame of 12 months. This includes those patients whose death is expected within hours or days; those who have advanced, progressive incurable conditions; those with general frailty and co-existing conditions that mean they are expected to die within 12 months (GMC, 2019).

Considering the overlap of palliative care and end of life care, amplified by the ambiguity of definitions as well as their interchangeable use within literature, this work will not attempt to distinguish between these terms.

## 1.5. Health Economics and Palliative Care

The care of terminal or highly symptomatic disease is expensive, with both a financial and capacity strain on individuals and local and national health systems globally. This is exacerbated by a demographic shift in age distribution; people live longer and have more health needs in later life (WHPCA, 2020).

It is possible to distinguish between different types of interventions at the end of life. Some of them, such as drugs that extend survival are considered by the National

Institute for Health and Care Excellence (NICE) and NICE's end of life criteria apply.

Several medical and technological advances expand treatment options, many at great cost (Abedini et al., 2019). For example, new anticancer treatments, like immunotherapies and targeted anticancer therapies improve progression-free survival, and sometimes overall survival, but significantly increase costs at end of life.

Drugs recently approved by NICE for poor prognosis cancers typically cost about an extra £50,000 for each quality of life-adjusted year (QALY) gained – a composite measure of individual quality of life and survival.

A QALY is defined as a *"measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health" (NICE, 2022c).*

Not all interventions set out to increase patients' remaining life time. A variety fall under the term 'supportive interventions' that don't affect survival and which are more classically considered palliative care. Another approach to improve care at the end of life is consideration of the configuration of services which are more the domain of health services research than health economics.

As the health care budget is constrained, hard choices must be made. Real patient care has numerous challenges and is limited by restricted healthcare budgets and an already stretched healthcare workforce. One important example is community care, which is largely dependent on the number of available informal carers, eg a family member.

Prioritising between this type of care and palliative or anti-cancer treatments is an

inherent tension. Health economic evaluations assist decision-making on a larger scale, like the choice between additional palliative care beds or new drugs or more intensive care.

## 1.6. Challenges of health economics in the final phase of life

As health economics informs decision-making, influencing the quantity, quality and sustainability of health care resources, it is imperative this methodology is applied to the highest possible standards. Within the UK, a standard approach to compare the cost-effectiveness of interventions has been established by decision makers like NICE. It relies on the costs to the NHS and social care, balanced against difference in QALYs.

For several reasons, this approach falls short when evaluating interventions at the End of Life.

- Firstly, a significant proportion of the important costs are likely be incurred outside of the NHS by the charitable sector, the welfare state, or the individual and their families and/or carers. These currently fall outside of a NICE standard economic evaluation.
- Secondly, it is inaccurate to define patient benefit using the same methodology applied in curative care given improved function or longer survival is not expected.
- Thirdly, the standard methods for quantifying health outcomes is problematic in end of life care as the patient needs/focus are different than in those expected to improve, meaning the QALY is the recommended tool for capturing health outcomes across different clinical and disease areas.

> However, the ability of the QALY to capture aspects of health important to patients in an end of life context has been questioned, given the aim at that juncture is neither improved survival nor function, but rather to to prevent and treat symptoms, preserve function, share decision-making and family care.

New research programs are testing different strategies of better capturing patients' priorities at the end of life such as burden of illness measures (BOI) or palliative-specific quality of life measurements e.g. Investigative Choice Experiments of CAPablility measures (ICECAP).

## 1.7. Why end of life care needs to be a key priority?

Worldwide, the financial cost to an individual with severe illness is significant. In the US, the risk of bankruptcy increases by 250 percent for those with a cancer diagnosis (Ramsey et al., 2013). Even in the UK where healthcare is free at the point of delivery, those with a cancer diagnosis were found, on a monthly average, to be £570 worse off (McMillan, 2017). The national palliative and end of life care strategy from the Scottish Government for 2016-2021 set out that by 2021 everyone in need of palliative care would have access to it (Scottish-Government, 2015).

Within the Scottish population of around 5.4 million a moderate increase in deaths can be observed over the last decade from 53,661 in 2011 (population of 5.3 million) to 63,587 in 2021 (NRS, 2021a).

Looking at a case example of why health economics is necessary, we can take end of life care within the UK. There is an urgent need for improvement given that in 2017, there were more than 607,000 deaths registered, which was a 1.6 percent

increase from the previous year and the highest number since 2003 (ONS, 2018). The palliative care funding review 2011 estimates an annual unmet palliative care need of 92,000 to 142,500 people within the UK (Hughes-Hallett et al., 2011).

Most people in the UK die in hospitals, despite it being the least preferred location (Bekelman et al., 2016; ONS, 2018). Many may have unnecessary clinical interventions unlikely to impact quality and/or length of life (Hughes-Hallett et al., 2011). Hospital care is expensive but comprehensive palliative care at home may also be costly.

In addition to the debate around where those at their end of life should be mainly cared for, the place of death and the question of who should be in charge of caring for the individual is also debated. It can be observed that in Scotland as well as in the whole of the UK there is an ongoing integration of health and social care (Finucane et al., 2019). Tailored end of life care integrated into public health care can reduce emergency hospital and ICU admissions and length of hospital stays (Morris, Fyfe, et al., 2013; Trtchounian et al., 2017).

A more personalised approach, therefore, has greater potential to avoid unnecessary resource use whilst simultaneously benefiting the patient.
In the UK, all of these issues are being tackled by a new national strategy to re-design palliative care services. But is there a need to prioritise, for example, between expensive new drugs with limited life prolongation and little evidence of improved symptom management or a basic human right to good end of life care (NHS-England, 2022; NICE, 2022b; Palliative and of Life Care Partnership, 2015)?

In line with national ambitions for personalised care, advanced care planning (ACP) is at the heart of this strategy, where patients should have realistic high quality

choices in their end of life. The strategy is shaped by six ambitions: each person is seen as an individual; each person gets fair access to care; maximising comfort and well-being; care is coordinated; all staff are prepared to care; each community is prepared to help. With equity of access as a core priority, it becomes obvious why health economics is fundamental for achieving these goals (Kirchhoff et al., 2012; Palliative and of Life Care Partnership, 2015). The national framework including the "Ambitions for Palliative and End of Life Care" was relaunched again in 2021 (Palliative and of Life Care Partnership, 2021).

The effectiveness of sustainable integrated palliative care programs as described by (Kaasa, Loge, et al., 2018) - including funding of end of life services - are well documented (Kaasa, Knudsen, et al., 2017) and it may be best to prioritise such interventions in a public health system.

*How much a society is able and prepared to spend on those who are sick and face approaching death may differ; views will vary across (and within) continents and countries and between faith and value systems (Round, 2016).*

The goal therefore should be to keep the financial burden of care of the dying on the healthcare system as low as possible without compromising the level of care or a person's quality of life. If the palliative care clinical community accepts available resources are constrained, then extensive work is necessary to better understand value at the end of life.

## 1.8. Focus on resource use, research questions and aims

Individuals approaching the end of life tend to have complex clinical and social care needs. Typically, multiple parts of the health and social care sector as well as the charitable sector act together in complex care provision. It can be challenging to understand which components of care are contributing towards costs and/or outcomes attributable to a specific individual.

For a full economic analysis, costs and outcomes are considered. The subsequent work focuses on the cost side of palliative and end of life care only, but might surprise with the complexity of the supposedly easier part of the puzzle.

As evidenced in the patient stories detailed in the preface "Imagine", there is more to the cost side than the identification of resources used within formal care, with subsequent summation of the costs. The costing profiles of patients are as diverse as the patients themselves, with added diversity influenced by the patient's family structure, demographics and access to health facilities frequently connected to regional factors.

Further, administrative datasets and clinical trials capture resource use in vastly different ways, leading to following questions:

> (i) What methods and data sources have been used to capture resource use and costs?
>
> (ii) What cost elements are essential when conducting health economic analysis in an end of life care setting?

This thesis seeks to gain insight into resource use collection and costing approaches at patients end of life with three main aims.

- Aim 1: *Understand the current landscape of resource use data collection and deriving costs at the end of life in a UK setting and define essential elements.*
- Aim 2: *Reflect on the challenges, benefits and limitations of using administrative data versus trial data in an end of life care setting, illustrated by case studies.*
- Aim 3: *Present potential solutions to challenges arising in collecting and analysing resource use and cost data of end of life care and provide recommendations for further research.*

The subsequent section presents an update of a systematic review, starting with an overview of the literature search strategy and its findings. It further provides insights on UK cost perspectives, collection of resource use data and approaches to deriving costs as identified by the literature.

## 1.9. Thesis structure and contribution

This thesis is focusing on the cost side of health economics in people's final stage of life. It includes several papers which by now are published or currently in the final step of the peer review process. The first part of chapter one (1.1 to 1.7) is the original version of the Editorial "Incompatible: End of Life Care and Health Economics" which appeared in its shortened form in BMJ-Supportive and Palliative Care in 2021. Chapter 2 includes and update of a systematic review published in 2018. Chapter 3 is based around routinely collected data, discussing the benefits and challenges administrative data provides. It includes two studies using administrative datasets. Chapter 4 is built around data collection and costing approaches of clinical trials and presents two applied examples. The discussion in chapter 5 draws from the learning of all chapters, includes key insights gained and suggestions for further research.

### Preview chapter 3 - Administrative data

The following two papers present research output generated through working with administrative data. The first one aimed to identify cost trajectories in the last year of life. Data included all decedents of the Scottish population, 60 years and older between 2011 and 2017. The second study took a narrower approach, investigating cancer patients only, but adding more depth by appending a cancer specific dataset. The latter study's goal was to provide better insight into care pathways of cancer patients at their end of life.

*Contribution to the papers presented in chapter 3*

I am first author in both of the presented papers. My contribution to the first one

*"Healthcare use and cost trajectories during the last year of life: A national population administrative secondary care data linkage study"* started just at the end of the data application process. I led on amending the research plan to the data we finally managed to secure access to, data cleaning, data analysis, drafting the paper, editing, gaining final approval and handling preprint, submission, review and re-submission process.

The second paper *"Variation in hospital cost trajectories at the end of life by age, multimorbidity and cancer type"* was generated out of new ideas, which arose during the analysis and interpretation of first study's output, as there were several questions we could not answer based on the data provided. In order to ensure that the second paper was of interest to a clinical and research audience, research objectives were set with the help of the clinicians involved in the wider study team. I led the rest of the study process (analysis, write-up) supported by some of the colleagues involved in the first study. Both papers were conducted in parallel with two English papers (links in Appendix 6.C.3) with all four of the papers being part of one bigger study funded by the Health Foundation.

My contribution to both of the English papers was limited to supporting the data analysis and data interpretation as well as assisting the drafting and editing process and approving the final version of the articles.

Conducting the Scottish and English studies in parallel, trying to perform a similar analysis (as far as the variables available and the costing processes in the countries allowed) led to some interesting insights. Unfortunately due to the big variation in the variables collected, the quality of the data and structural difficulties, such as working in different safe-havens, the idea of a comparison paper needed to be rejected. The first study was published in BMJ-Supportive and Palliative Care in

2021, the second study was accepted in IJPDS (International Journal of Population Data Science) in October 2022. Both papers were previously published on the preprint-server MedRxiv.

## Preview chapter 4 - Clinical trials

Chapter 4 presents two clinical trials which serve as examples for primary cost collection and demonstrate different costing approaches. These trials additionally demonstrate some over-the-time progress within the field of health economics, as health economics more recently became an integral part of clinical trials due to a change in funder requirements. Whereas the first trial (EPAT) *"Does an institutionalised approach to cancer pain assessment and management result in more individualised and cost efficient care?"* did not originally include health economics, hence the analysis was performed after the clinical outcomes of the trial were already published, the second trial (ENeRgy) *"A randomized, feasibility trial of an exercise and nutrition-based rehabilitation programme (ENeRgy) in people with cancer"* showcases the density and quality of information which can be captured if health economics is integrated from the planning phase of a trial.

The study population in the subsequent trials is substantially different from the patients included in the studies in chapter 3. Whereas chapter 3 presents two whole population studies, chapter 4 includes two clinical trials. The first study included 940 cancer patients across 19 UK cancer centres; the second, a feasibility trial, included 45 patients from hospices. Further there are differences around timing, with chapter 3 focusing on the last 12 month of life, whereas patients in EPAT were selected due to an inpatients stay in a cancer centre and patients in ENeRgy were eligible if their remaining survival was predicted to be more than 3 months.

*Contribution to the papers presented in chapter 4*

I worked as the assigned trial health economist in both of the studies. My contribution varied considerably, mainly due to the start of the collaboration and is specified below.

My involvement within the EPAT study started after the results from the clinical study were already published. We (Peter Hall and myself), worked with the original study team to conceptualise a study looking at the resource use and costs, which were captured but not analysed as part of the primary study.
Despite it being unusual and not necessarily best practice we applied for a data excerpt to get some information on the variables collected (and the quality of the data). After getting an idea of the data and speaking to the a number of researchers involved in the initial trial, we developed a strategy and drafted a health economics analysis plan (HEAP).
After acquiring access to the full data, whilst supporting data management in this process the data analysis was conducted. Data interpretation and the write-up of the health economic sections were led by myself. Further I supported the writing process of the introduction and discussion section, which was led by Marie Fallon. The paper is in the final stage of the review process at the Journal of Clinical Oncology. The paper presented in the thesis is the clean version of the revised manuscript. A short section describes the challenges of "piggybacking" a health economic analysis on (already published) clinical trials.

In the ENeRgy trial, I was involved from the conceptualisation and trial design phase; therefore, health economic considerations were taken into account in each step along the process. I led on the development of the trial specific health economics

questionnaire, drafted a health economic analysis plan aligned to the statistical analysis plan (SAP), analysed the data and wrote up the health economic results.
The published paper includes the clinical results as well as qualitative aspects and the health economics part. In order to stay in line with the journal's requirements, the latter was shortened in the paper. The thesis includes a long version of all health economic considerations within the ENeRgy trial. The protocol and the published paper are included in the appendix 6.D.2.

# Chapter 2

## Literature on Resource use and Cost

In order to gain first insights into the wider topic connected to the research question: *What cost elements are essential when conducting health economic analysis in an end of life care setting?*, an update of a systematic review was completed.

## 2.1. Explore literature on costs

To avoid replication of existing research, the electronic databases CINAHL, Cochrane and Medline were searched for existing systematic reviews. This search identified the systematic review *"What cost components are relevant for economic evaluations of palliative care, and what approaches are used to measure these costs?"*, by Gardiner, Ingleton, et al. (2017).

This review included all of the keywords and MeSH terms (Medical Subject Headings) a systematic review suitable for this thesis required, and partially answered the research questions of interest. The only identified negative, for the purpose of this thesis, was its wider geographical scope. After refining the search strategy to focus on the UK, the systematic review *"What is the cost of palliative care in the UK?"* was identified (Gardiner, Ryan, et al., 2018).

Despite the review's title suggesting a better fit of the first review to answer the research question at hand, the second review includes approaches to capturing resource use and costing methods in the paper. Further, when looking at the search terms and inclusion/exclusion criteria it can be seen, that the search strategy is identical to the first review, with the sole distinction of the latter being limited to UK based studies.

Given these two systematic reviews focused on the research questions of interest, it was unlikely that a new review would add substantially to the evidence base.

Nevertheless, the search was restricted to papers published prior to October 2017, therefore an update of the latter review was undertaken.

## 2.2. Methods

More recent publications were identified by applying the exact same search strategy used by Gardiner, Ingleton, et al. (2017) and Gardiner, Ryan, et al. (2018). The protocol of the search strategies can be found in Appendix 6.B.1.
Electronic databases searched were CINAHL, Cochrane, PSYCHINFO and Medline. The applied inclusion/exclusion criteria, which were again taken from Gardiner, Ryan, et al. (2018) are listed in the table below.

Table 2.1. Inclusion and Exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Papers must report costs of a palliative care approach (defined as a comprehensive package of care incorporating specialist and/or generalist elements).<br>• Papers must report on any cost (full economic costs) of palliative care, OR costs in more than one setting or from the viewpoint of more than one provider.<br>• Studies providing data from the UK or countries within the UK.<br>• Original research (i.e. involving independent data collection)<br>• Papers relating to adults | • Literature reviews<br>• Unpublished manuscripts, conference abstracts, posters and other empirical work not published in full<br>• Non-empirical articles e.g. discussion papers, letters, editorials<br>• Papers only reporting on costs which relate to specific element of care or specific interventions e.g. costs of Advanced Care Planning/hospice care/home care etc.<br>• Papers which report how much was paid for palliative care (by commissioners), as opposed to how much palliative care cost.<br>• Non-English language papers |

Data extraction included next to the author and date of publication, the categories of the economic perspective, the individual study's patient group, the time period (included in the analysis), the source of resource use data, the applied unit costs and final costs. Data extraction tables are provided in the results section.

The new literature search included publications from October 2017 until October 2021.

## 2.3. Results

The results are grouped into several categories, namely search results, health care perspectives, study periods, sources of activity data and costing sources.

### 2.3.1. Search Results

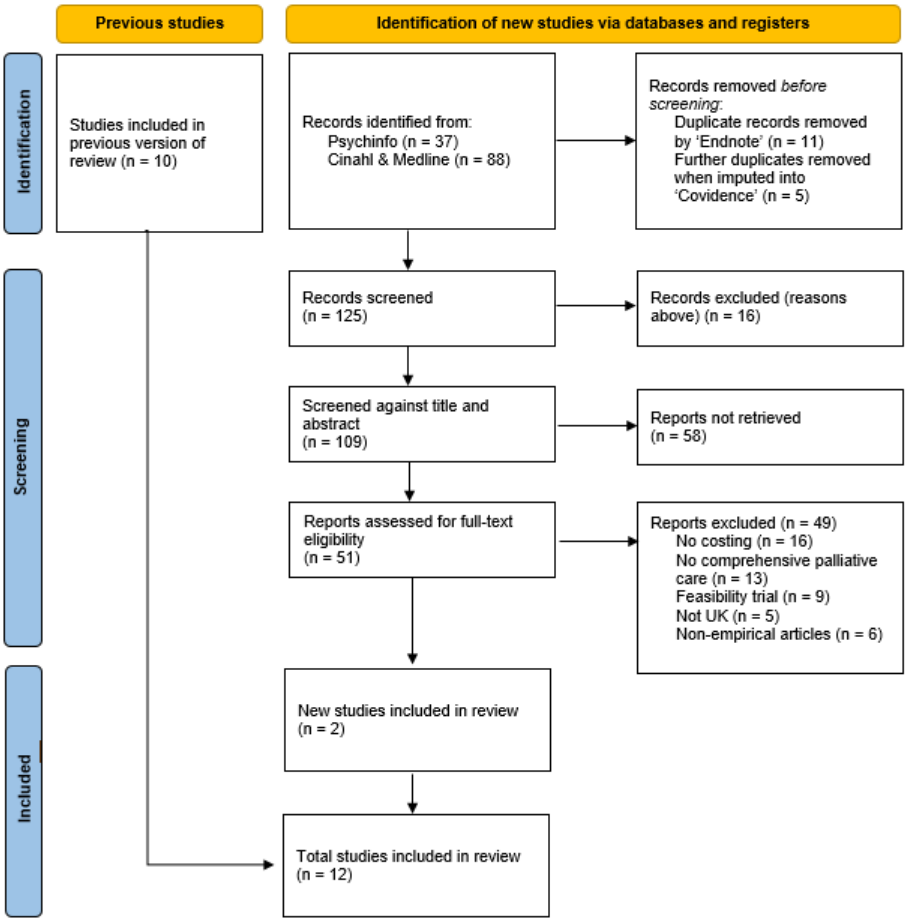
The search in Psychinfo and 'Cinahl & Medline' (see Appendix 6.B.1) identified 37 and 88 papers respectively. No Cochrane review matching the search terms had been published within the set period.
All references were initially imported into "Endnote" and 11 duplicates were removed. The remaining 114 references were transferred into the "Covidence" software. Covidence is a software assisting the systematic review process, freely available via the library services of the University of Edinburgh.
Five more duplicates were identified by Covidence and were removed. Subsequently 109 studies were screened against title and abstract of which 51 were assessed for full-text eligibility.

The inclusion/exclusion criteria applied, were in line with those laid out in the original review by Gardiner, Ryan, et al. (2018). Of the remaining 51 studies, 49 were excluded due to a variety of reasons specified in the subsequent flow chart using the structure as outlined by Boutron et al. (2021). This left 2 additional papers for final inclusion, hence the updated review is presenting information from 12 papers.

Of the twelve studies included, six were cross-sectional or cohort studies, four based on modelling and two drew on trial data. The subsequent section presents the results of the review in a structured way, starting with economic perspectives rele-

vant within the UK and related costs, the study period reported upon, commonly captured resources and a description of the various sources of activity data.

Figure 2.1. PRISMA flow diagram - Literature search October 2017 to October 2021




## 2.3.2. Health Care Perspectives

There are several different perspectives which can be adapted when conducting health economic evaluations.

*Short Digression*: The perspective refers to the viewpoint taken when deciding on the health benefits and the costs/resource use included in an evaluation. Following the structure of the paper by Garrison Jr et al. (2018), commonly adapted angles are those of:

a) the payer perspective (relevant in non single-payer systems),

b) the health system perspective (NHS in UK context),

c) the patient perspective which is adding the patient and unpaid caregiver "time cost" as well as the transportation costs and

d) the societal perspective which is very broad as it additionally includes the impact of an health event on consumption, productivity and a variety of relevant but not directly health care related domains into account.

### 2.3.3. Substantive results

All twelve studies within the review included elements relevant to the health system perspective in a UK setting, the NHS-perspective (Bardsley et al., 2010; Coyle et al., 1999; Dzingina et al., 2017; Georghiou and Bardsley, 2014; Guest et al., 2006; Hatziandreu et al., 2008; Hollingworth et al., 2016; Jayatunga et al., 2020; Johnston et al., 2012; McBride et al., 2011; Round et al., 2015; Yi et al., 2020).

Eight out of the twelve studies (Bardsley et al., 2010; Coyle et al., 1999; Dzingina et al., 2017; Georghiou and Bardsley, 2014; Jayatunga et al., 2020; McBride et al., 2011; Round et al., 2015; Yi et al., 2020) also included some social care costs, taking a slightly broader approach, coming under the NICE standard NHS- and social care perspective, though none of them was broad enough to be categorised as a patient/or societal perspective.

Two studies, Dzingina et al. (2017) and Round et al. (2015) additionally included elements of informal care and other elements such as "over the counter" medication. As these studies include secondary care data, data on social care and informal care, they are the closest examples of adopting a patient perspective.

### 2.3.4. Study period

The time-frame considered within the studies varied considerably, ranging from one week, as in Coyle et al. (1999), to several years, as in Johnston et al. (2012). Commonly used time frames were three months such as by Hollingworth et al. (2016) and Yi et al. (2020), 90 days as by Georghiou and Bardsley (2014) and a year.

Four out of the twelve studies considered a time period of one year (Bardsley et al., 2010; Hatziandreu et al., 2008; Jayatunga et al., 2020; McBride et al., 2011). Nevertheless a similar time period is in no way allowing comparability of costs as will be seen in the context of each study.
Whilst Hatziandreu et al. (2008) and McBride et al. (2011) were looking at decedents with cancer and/or organ failure, Bardsley et al. (2010) and Jayatunga et al. (2020) included "any palliative care patient".

Two studies used the initiation of strong opioids as a starting point, describing an expected survival of 243 days as in Round et al. (2015) and 301 days of expected survival in Guest et al. (2006).

Table 2.2. Extraction table 1

| Author, date | Perspective | Patient group | Time period | Costs |
|---|---|---|---|---|
| Coyle, 1999 | NHS, social care | Non-curative | One arb. week | Total: £4140 |
| Guest, 2006 | NHS | Cancer | Opioids - death (301 days) | Total: £4237 |
| Hatziandeau, 2008 | NHS | Cancer & organ failure | Last year of life | Total: £38377 (!19188); Cancer: £16552; Organ failure: £21825 |
| Bardsley, 2010 | NHS, social care | Palliative patient | Last year of life | Total: £10318; Hospital: £6957; Social care: £3361 |
| McBride, 2012 | NHS, social care | Cancer & organ failure | Last year of life | Total: £19451; Cancer: £16952; Non-cancer: £21950 |
| Johnston, 2012 | NHS | Advanced melanoma | 3 years post diagnosis \| death | Total: £9091; Hospital: £6875; Hospice: £1737; Outpatient: £497 |
| Georghiou, 2014 | NHS, social care | Palliative patient | Last 90 days | Hospital: £4932; Social care: £1096; Community nurse: £305; GP: £161 |
| Round, 2015 | NHS, charity, social- informal care | Cancer | Opioids - death (243 days) | Total: £10311; Health care: £4433; Social care: £1906; Charity: £487; Informal care: £3396 |
| Hollingworth, 2016 | NHS | Heart failure | Last 3 months | Total: £9198 |
| Dzinga, 2017 | NHS, social care, informal care | Advanced disease \| refactory breathlessness | 3 month prior trial entry | Total: £12444; Formal care: £3518; Informal care: £8926 |
| Jayatunga, 2020 | NHS, social care | Any end of life care patient | Last year of life | Total: £11586; Outpatient: £390; Social care: £2483; Un/planned hospital: £5109/£2081; Primary: £1170; Emergency: £354 |
| Yi, 2020 | NHS, social care | Palliative patient | Last 3 months | Total: US$13206; non-cancer: US$13844 |

### 2.3.5. Resource use data collection - source of activity data

In terms of source of activity data, studies demonstrated considerable variation. Formal hospital based health care was included in all studies and was frequently based on administrative data, such as 'Hospital Episode Statistics' (HES). Hospital care activity collected included inpatient, outpatient and daycase activities and if available, visits to palliative care outpatient clinics. Mainly collected were hospital admission, bed days, and inpatient procedures such as chemotherapy, radiotherapy and surgical procedures, as well as investigation, laboratory and diagnostic activity costs (Hatziandreu et al., 2008; Hollingworth et al., 2016; Jayatunga et al., 2020; McBride et al., 2011; Round et al., 2015).

The three following studies by Dzingina et al. (2017), Johnston et al. (2012), and Yi et al. (2020) additionally used data generated through clinical trials. Questionnaires were filled in by patients and/or relatives, clinicians and other health professionals and subsequently collected by the trial team.

In addition to hospital-based care, eight studies included components of social care and/or community care, including non-NHS costs i.e. those incurred by the local authorities who provide care. Generally, these costs relate to a mix of community care (which includes aspects of primary care such as GP visits) and home based care and tended to include care provided in long term care facilities, for example residential care and nursing home care (Bardsley et al., 2010; Coyle et al., 1999; Dzingina et al., 2017; Georghiou and Bardsley, 2014; Jayatunga et al., 2020; McBride et al., 2011; Round et al., 2015; Yi et al., 2020).

Activity data were captured using a variety of approaches such as patient reported measures (Dzingina et al., 2017; Johnston et al., 2012; Yi et al., 2020), published literature as in Round et al. (2015), data access gained directly from providers as

in Coyle et al. (1999) and Georghiou and Bardsley (2014) or local authority client management systems such as in Bardsley et al. (2010) and Jayatunga et al. (2020).

Hospice and specialist palliative care activity was captured less frequently (Georghiou and Bardsley, 2014; Jayatunga et al., 2020; Johnston et al., 2012; Round et al., 2015). Nevertheless, if included, costs added up to considerable share. Hospice cost reported by Johnston et al. (2012) for example comprised just under 20% of the overall care costs.

As mentioned above, two studies included elements of informal care (Dzingina et al., 2017; Round et al., 2015), which made up a significant proportion of the costs, namely 33% and 72% respectively. In Round et al. (2015) data on informal care was provided by a charity (Marie Curie) whilst Dzingina et al. (2017) used patient reported data, captured in the 'Client Receipt Inventory'.

Table 2.3. Extraction table 2

| Author, date | Source of resource use data | Unit costs |
|---|---|---|
| Coyle, 1999 | From service providers; information on resource use & length of visit | PSSRU Unit costs; other sources where PSSRU costs were unavailable |
| Guest, 2006 | Primary and secondary care: DIN-Link database | Hospital cost: PSSRU Unit costs; Drugs: MIMS & Drug tariff |
| Hatziandeau, 2008 | Hospital activity: HES, hospice use: MDS | Prices from Coyle 1999 |
| Bardsley, 2010 | Social care: local authority client management systems; hospital activity: SUS; GP use: GP register information | PSSRU Unit costs |
| McBride, 2012 | Hospital activity: HES, hospice use: MDS | Hospital & hospice costs: Coyle 1999; Residential care & ambulance: PSSRU Unit costs |
| Johnston, 2012 | Directly from patients | Hospital costs: NHS reference costs; Hospice costs: Hatziandreau 2010 & Consumer Price Index |
| Georghiou, 2014 | GP: READ, Community nurses: local data, Social care: linked HES/social care/mortality dataset, Hospice: Marie Curie, Hospital activity: HES | Hospital costs: NHS reference costs; GP, nursing & social care: PSSRU Unit costs; Hospice: Marie Curie |
| Round, 2015 | Estimates from published lit., hospital activity: HES, hospice care: Marie Curie | Hospital & social care: NHS reference costs & PSSRU Unit costs; Hospice: Marie Curie; Informal Care: ONS average earnings |
| Hollingworth, 2016 | Hospital activity: HES | Hospital & social care: NHS reference costs & PSSRU Unit costs; Drugs: NHS prescription costs |
| Dzinga, 2017 | Patients completed the Client Services Receipt Inventory | Hospital & social care: NHS reference costs & PSSRU Unit costs; Informal care: PSSRU unit costs (home care worker - proxy informal care) |
| Jayatunga, 2020 | From health care providers, local government services & health commissions | Hospital & social care: NHS reference costs & PSSRU Unit costs |
| Yi, 2020 | Trial data | Hospital & social care: NHS reference costs & PSSRU Unit costs |

### 2.3.6. Costing sources

There was some consistency in the costing sources. Seven studies (Dzingina et al., 2017; Georghiou and Bardsley, 2014; Hollingworth et al., 2016; Jayatunga et al., 2020; Johnston et al., 2012; Round et al., 2015; Yi et al., 2020) used NHS reference costs for costing inpatient activity and all except Johnston et al. (2012) used the Unit Costs of Health and Social Care (PSSRU - Personal Social Services Research Unit) in one way or another.

If hospice costs were included they where based on information directly provided from Marie Curie as in Georghiou and Bardsley (2014) and Round et al. (2015) or based on the publication by Coyle et al. (1999) as by Hatziandreu et al. (2008), Johnston et al. (2012), and McBride et al. (2011).

For costing informal care, as included by Dzingina et al. (2017) and Round et al. (2015), first used average earnings as provided by the Office for National Statistics (ONS) whilst later used 'cost of a home care worker' as provided in the PSSRU to estimate the cost of informal care.

Two of the twelve studies included drug costs. Hollingworth et al. (2016) used NHS prescription costs as a source of unit costs, whilst Guest et al. (2006) used MIMS (Monthly Index of Medical Specialties- Database of Prescription and Generic Drugs) and the Drug Tariff produced on behalf of the Department of Health and Social Care likewise updated on a monthly basis.

## 2.4. Discussion

As demonstrated in the results section, similar study periods are no guarantee for conformity in costs. It further needs to be noted that the costs presented in table 2.2 refer to the costs as presented in the studies identified by the literature review. These costs are not meant for direct comparison as the studies are featuring different perspectives, time periods, patient cohorts, price years and reflect the big variety in costing sources included and costing methods applied. Looking at the studies by Round et al. (2015) and Guest et al. (2006), a significant difference in costs can be observed with £10,311 versus £4,237. One potential explanation could be based on patient groups, which was not the case as both studies included cancer decedents only. The main difference found was the economic perspective chosen.
Whilst Round et al. (2015) included NHS, social care, charitable sectors and informal care, the results from Guest et al. (2006) were limited to NHS costs only. Looking further into the breakdown of cost reported by Round et al. (2015) it was observed that when looking at NHS costs only, these added up to £4,433 out of the £10,311, compared to £4,237 by Guest et al. (2006). In this case the disparity in the reported costs could be explained by the perspective taken.

When comparing the studies by Hatziandreu et al. (2008) and McBride et al. (2011) finding an explanation for the cost difference between £38,377 and £19,451 was challenging as the latter even included social care costs on top of NHS costs, thus would be expected to be more expensive.
Looking at it in more detail, studying the source of activity data, it was found that both used HES data for hospital activity and the data from the 'National Council of Palliative Care' for capturing palliative care activity.

Another factor possibly explaining some of the variation could be the source of unit costs. As both based their hospital and hospice costs on the publication by Coyle et al. (1999), this can be ruled out.

Looking at the costs for cancer patients and organ failure patients separately, it was found that similar values were reported with £16,552 and £16,952 for cancer and £21,825 and £21,950 for organ failure. It was obvious that there is a miscalculation in the publication by Gardiner, Ryan, et al. (2018) in the way in which the costs of cancer patients and organ failure patients were summed up, which therefore ended up reporting £38,377 (£16,552 + £ 21,825), whilst the "true" costs were a close match.

### 2.4.1. Resource use data collection

Across the studies, resource use was captured in various ways. It depended mainly on the study design (clinical trial or study based on administrative data) and the economic perspective taken.

As mentioned in the results, all of the included studies used care activity related to formal (hospital-based) health care, mainly including treatment costs. Treatment costs were commonly split into resource use and costs associated with managing certain diseases including hospital admissions, outpatient attendances, the costs of medicine and the costs of managing possible adverse events caused by treatments. The health service payer perspective excludes patients' costs of obtaining care, such as transportation, over-the-counter purchases, co-payments and time off work.

Within the health service payer perspective cost aggregation, hospital-based activities, particularly inpatient stays are the key-costs, and are thought to account for the largest share of the overall health care costs. Further, they are meant to be the most straightforward care activity to capture, as a great share of them are automatically

recorded in hospital data systems. Nevertheless, there is some variation within the UK in terms of health care related activities and connected costs which are routinely captured. Further there are differences in how the various systems record and process this data (Gardiner, Ingleton, et al., 2017; Geue, Lorgelly, et al., 2015).

Social care and community based care can include primary care such as GP visits, phone consultations and home visits, as well as home visits from other care professionals such as nurses, social workers, home care and other allied health professionals' home visits such as Physiotherapists and Occupational therapists. Some studies included medications as well as diagnostic tests and laboratory costs. Others were more focused on the stays in long term care facilities and care homes and personal support for patients at home such as help with patients Activities of Daily Living (ADLs), for example help with grocery shopping and cleaning, and Instrumental ADLs (IADLs) such as supporting patients with bathing, dressing etc.
The inclusion of community care in studies adds an additional layer of complexity as social/community care funding is, similarly to hospital-based care, not uniform across England and Scotland nor even within the countries. Depending on a variety of factors, individuals might pay themselves for their own home/personal care and nursing home fees (Gardiner, Ingleton, et al., 2017; Gardiner, Ryan, et al., 2018).

As hospice-based care and specialist palliative care are frequently co-funded by public health care systems and charities, the cost components were dependent on the study and considered as part of either, social care or hospital care. There are no clear reporting guidelines for hospice-based activities. Within the UK there is a similar structure and breakdown of costs as hospital inpatient care, with main components being inpatient hospice stays and inpatient hospice days, as well as home visits from specialist palliative care (Gardiner, Ingleton, et al., 2017). Hospice-based care

activity captured within clinical trials tends to break down care components into much more detail and might include elements of personnel costs, medical supplies, procedures, medications and many other categories.

The informal care activity included in the studies, reported costs relating to home caregivers and out-of-pocket expenses experienced by the caregiver or the person cared for. A rarely considered issue are potential equity concerns connected to informal care resulting in a potentially huge financial burden which in itself is connected with negative (health) outcomes for patients and carers (Gardiner, Robinson, et al., 2020). Nevertheless research by Higginson et al. (2020) suggests that informal care can be facilitated in a way that is not necessarily detrimental to carers and patients, if informal carers are supported appropriately.

None of the studies included in the systematic review incorporated the wider societal perspective, as none of them included a comprehensive spectrum of opportunity costs such as indirect costs like patients and/or caregiver's time costs and income loss. Of particular economic relevance, the societal perspective includes time off work 'absenteeism' for patients and family members as well as a productivity loss due to a reduced working capacity even when being physically at work 'presenteeism' (Brick et al., 2017; Dzingina et al., 2017; Gardiner, Brereton, et al., 2014; Rowland et al., 2017; Tanuseputro et al., 2015).

The perspectives are difficult to delineate from each other as the boundaries are strongly dependent on the way health and social care systems are structured. This is further complicated by the cultural context within a country, such as "gender roles and expectations", culture of inclusion of those close to death or avoidance, family structures and many other aspects. The patient perspective seems to leave

most room for interpretation as it can include elements of all perspectives. Due to the blurred boundaries between the economic perspectives and connected costs, an in-depth look at the definition of the perspective in the individual papers is recommended prior to comparing study outcomes.

### 2.4.2. Costing sources

Hospital based activities are routinely collected, however there are differences across the UK. There is considerable variation in the collection and recording of the resources. Subsequently, different methods are applied for deriving the costs.
In England, Hospital Episode Statistics (HES) data are frequently used as in Curie (2012), Dzingina et al. (2017), Georghiou and Bardsley (2014), Hatziandreu et al. (2008), Hazra et al. (2018), Hollingworth et al. (2016), McBride et al. (2011), and Round et al. (2015), with associated costs usually taken from the National Tariff or NHS Reference Costs (NHS-Digital, 2021a; NHS-Payment-System, 2021).

Another way to understand resource use within secondary care in England is the use of the NHS Secondary Users Service (SUS) data published by NHS-Digital (2021b), which is a comprehensive repository for English healthcare data used for reporting and analysis within the NHS. SUS is mainly used for healthcare planning, service commissioning, national tariff reimbursement and policy development (Bardsley et al., 2010). Nevertheless, access is restricted and therefore the use for research very limited.

In Scotland, hospital-based data can be linked to other health datasets via the unique Community Health Index number for each patient. Linkage can be established between outpatient (SMR00), inpatient and day case (both SMR01) provided by ISD (2021) and the Scottish Morbidity Record (NRS death) provided by the

National Records of Scotland (Georghiou and Bardsley, 2014; NRS, 2021b). These data can further be linked to the Scottish Cancer Registry (SMR06) and to SMR04, with the later including data on hospital episodes related to mental health (ISD, 2021). The associated costs are usually taken from the Scottish health service costs ofter referred to as the "Scottish cost book" (PHS, 2021). All these costs are based on national average unit costs for specific service codes (Bardsley et al., 2010; Dzingina et al., 2017; Georghiou and Bardsley, 2014; Hazra et al., 2018; Round et al., 2015).

A dataset for community care is in development and will be costed by the PSSRU - Personal Social Services Research Unit (PSSRU, 2021b). Due to the absence of a national dataset, studies derive community care costs in different ways such as using local data recording of community nursing as in Georghiou and Bardsley (2014) or using social care resource from local authority client management systems see Bardsley et al. (2010). A number of studies used the Client Services Receipt Inventory (CSRI) to comprehensively record the received resources (PSSRU, 2021a). In the CSRI the unit costs are once more derived using the PSSRU costs (Dzingina et al., 2017).

Historically hospice use was taken from the Minimum Dataset (MDS) held by the National Council of Palliative Care as used in Hatziandreu et al. (2008) and McBride et al. (2011) which was later replaced by the National End of Life Care Intelligence Network (NEoLCIN) (NEoLCIN, 2021).

A considerable amount of care funding at end of life comes from charities. These data are difficult to capture but can be included if the charities themselves provide the data; for example, Marie Curie supplied data for the studies by Georghiou and

Bardsley (2014) and Round et al. (2015). Note that cost data provided by charities such as Marie Curie frequently include various different costing sources. Whilst data linked to the Marie Curie Nursing Service is calculated based on the services provided by Marie Curie based services, everything outside their scope is based on cost estimates such as PSSRU and others (Curie, 2012).

### 2.4.3. Limitations

Sticking to the exact same search strategy as used by Gardiner, Ryan, et al. (2018) limited the included literature to studies reporting on costs and therefore excluded potential studies of interest which were reporting on resource use only. Further it is possible that sticking to the same criteria led to the exclusion on some palliative care trials which potentially were of interest to the wider project.

The big variety of patient cohorts included in the studies especially when looking at the variety in the included patient groups (all non-curative patients, cancer, cancer and organ failure, health failure,...) is making a comparison of costs impossible. With some studies being based on clinical trial data and others including administrative data the likelihood of the sample of patients included in those studies being representative of the general end of life care population is fluctuating.

## 2.5. Conclusion

This updated review provides some insights into the complexity and heterogeneity of the collection of care activity and costing approaches at the end of life. Whilst hospital-based care is frequently captured, followed by social care and community care, and will benefit from the development of a national dataset, informal care, hospice-based care and the contribution from charities are commonly neglected.

Further heterogeneity is found in the source of activity data, showing not only differences between routinely collected data and trial based data collection, but also regional variations within the UK such as HES data being restricted to England, thus impeding comparison with Scottish studies.

Another factor complicating deriving costs at the end of life in a UK setting is the lack of guidelines regarding the source of unit costs. Whilst most studies use costs from PSSRU in one way or another, there is no standardised approach to costing end of life care activity.

Findings from the two newly included papers are in line with the results by Gardiner, Ryan, et al. (2018). Jayatunga et al. (2020) and Yi et al. (2020) add one trial and one big data study, with time periods of the last three months versus the last year respectively. Overall the same shortcoming was concluded by Gardiner, Ryan, et al. (2018) as it remains challenging to *"accurately estimate costs in these settings, namely (due to) the lack of standardised national datasets, the lack of methodological guidance, and a complex picture of care provision in palliative (end of life) care."*

# Chapter 3

## Estimating resource use and costs - Routine data

## 3.1. Using Administrative Data

Exploiting routinely collected data for research has become increasingly popular over the last few decades. Nevertheless it comes with as many challenges as advantages. This chapter will highlight the benefits and limitations of using routinely collected data, and describes the costing approaches identified in the literature, before showcasing two practical examples of administrative data studies. The chapter's last part presents insights gained by working with big data and navigating through the corresponding challenges.

### 3.1.1. Benefits of using routinely collected data

There are multiple reasons why routinely collected data are a great resource for research. One of the most important points as argued by Bain et al. (1997), is that the data are theoretically readily available and come at a relatively low cost, as the structure for data collection is already in place.

Another crucial factor is that administrative datasets have a low risk of sampling errors and selection bias due to the large numbers of records (Bain et al., 1997; Hemkens et al., 2016). If the routine dataset in use covers the whole population, it comes with further benefits as, for example, incidence and prevalence rates are exact, which theoretically makes confidence intervals redundant. Nevertheless population data are commonly assumed to be just a sample of a larger population and therefore confidence intervals are presented (Bain et al., 1997).

A major benefit is that administrative datasets commonly span several years, which allows for observing developments over time. Further it allows for observing 'natural experiments' such as changes due to huge policy interventions and/or a health

crisis in a country.

Further, data include diversely recorded items and cover a wide range of items. Bain et al. (1997) highlight that this enables researchers to delve into rare topics. At the same time they warned that *"care must be taken, however, not to 'dredge' the data for associations which have no prior hypothesis or biological basis."*

In an end of life care setting one of the main arguments for using routinely collected data is that it is not adding any additional burden on the patients, relatives and/or caregivers. Whilst filling in questionnaires and/or being interviewed can be experienced in a positive way, as it allows patients and caregivers to openly speak about potential struggles, challenges and needs, it can be experienced as an additional burden.

Hemkens et al. (2016) summed up most of the arguments in favour for an increased use of routine data as follows: *Data collection under real-world circumstances maximizes representativeness and generalizability, minimizes costs and effort, and allows the capture of information in large populations and many clinical events in large datasets that are continuously updated and cover long periods.*

But is routinely collected data already fit for purpose? This still applicable question was already asked by Bain et al. (1997), who identified potential gaps in data density, spoke about issues arising when combining data from different sources and highlighted potential computational restraints. Additionally, they noted the importance of the choice of the right software and confidentiality and ethical issues as the main challenges.

### 3.1.2. Weaknesses of routinely collected data

Despite the obvious benefits of exploiting routinely collected data, using them for research comes with some major challenges. The most common short-comings as described in the literature are subsequently outlined, most of which were experienced in the studies included.

Firstly Hemkens et al. (2016) argue that some routinely collected datasets are not representative. They refer to situations in which data collection is biased through to inequities in access to treatment such as the ability to pay.
In the UK, where healthcare is free at the point of access, routinely collected data should not suffer from bias, given the ability to pay and/or access to care.
Nevertheless, routinely collected data are frequently restricted to a specific care setting such as hospital-based care interventions, hence not showing potential substitution effects through an improved primary or community care.
The subsequent studies had no sampling bias as the whole Scottish population was included, albeit limited to secondary health care only. The parallel conducted English studies are known to include some selection bias with the London-based population being over-represented and data from the north of England being less representative.

Additionally, introducing and maintaining an infrastructure for routine data collection is costly and time consuming (Hemkens et al., 2016). If data need to be stored in a safe data environment and later needs some changes to guarantee data security or linkage to be fit for research purposes, costs can be considerable. Changes in medical coding and reimbursement systems can further complicate the matter as they might have a knock-on effect on the underlying coding in the system.

Another factor mentioned by Hernán and Robins (2006) and Schneeweiss and Avorn (2005) is the observational nature of routinely collected data as it is a built-in limitation for the study of treatment effects. *Which treatment is chosen depends on various known (e.g., severity of disease) or unknown factors that may be associated with the outcome. Such confounding by indication can invalidate real-world observations.*

Further Hemkens et al. (2016), argue that whole population data or even datasets with a large enough sample size run the risk of presenting *"statistically significant false-positive and false-negative results."*

In addition, it is challenging to identify bias introduced through data processing, data linkage, classifying items and possible over/under-reporting due to faulty data collection tools. (Bohensky et al., 2010; Schneeweiss and Avorn, 2005).

Overall it can be stated that routinely collected data can be a valuable source for research as it includes great breadth and diversity of data. Due to the impossibility of understanding the driving forces behind observational data (and recognising potential bias), research based on administrative data is useful for finding correlations but a more thorough research design is needed to study causality.

## 3.2. Approaches to deriving costs for routinely collected data

Not all care activity within the UK is routinely collected. There are reliable data available for hospital-based activities and, depending on the location within the UK, primary care data might not just solely be collected but also be usable for research.

## Hospital-related resource use data

Hospital-based activities are routinely collected, however there are differences across the UK. Firstly, there is considerable variation in the collection and recording of the resources. Subsequently, there are different methods used when deriving costs. In England, Hospital Episodes Statistics (HES) data are frequently used and includes inpatient and outpatient activity as well as A&E visits (Curie, 2012; Dzingina et al., 2017; Georghiou and Bardsley, 2014; Hatziandreu et al., 2008; Hazra et al., 2018; Hollingworth et al., 2016; McBride et al., 2011). Associated costs are usually taken from the National Tariff or NHS Reference Costs (NHS-Digital, 2021a; NHS-Payment-System, 2021).

Another way to understand resource use within secondary care in England is the use of the NHS Secondary Users Service (SUS) data NHS-Digital (2021b), which is a comprehensive repository for English healthcare data used for reporting and analysis within the NHS. SUS is mainly used for healthcare planning, service commissioning, National tariff reimbursement and policy development (Bardsley et al., 2010). Nevertheless, access is restricted and therefore the use for research is very limited.

In Scotland, hospital-based data can be linked to other health datasets via the unique Community Health Index number for each patient. Therefore, linkage can be established between outpatient (SMR00), inpatient and day case (both SMR01) ISD (2021) and the Scottish Morbidity Record provided by the National Records of Scotland (NRS death) Georghiou and Bardsley (2014) and NRS (2021b). These data can further be linked to the Scottish Cancer Registry (SMR06) and to data on hospital episodes related to mental health (SMR04) (ISD, 2021). The associated

costs are usually taken from the Scottish Health Service costs (Scottish cost book) (PHS, 2021). The costs are based on national average unit costs for each service code (Bardsley et al., 2010; Dzingina et al., 2017; Georghiou and Bardsley, 2014; Hazra et al., 2018; Round et al., 2015).

## Community care

In England, a dataset for community care is in development and will be costed by the Personal Social Services Research Unit (PSSRU) (PSSRU, 2021b). Due to the absence of a national dataset, studies so far derived community care costs in a variety of ways such as using local data recording of community nursing as in Georghiou and Bardsley (2014) or by using social care resource from local authority client management systems see Bardsley et al. (2010). A number of studies use the Client Services Receipt Inventory (CSRI) to record comprehensively the received resources (PSSRU, 2021a). In the CSRI the unit costs are once more derived using the PSSRU costs (Dzingina et al., 2017).

In Scotland a primary care dataset SPIRE (Scottish Primary Care Information Resource) is in development and theoretically available for research, however it is not yet fully linkable to secondary care data (PHS, 2022).

## Hospice and Specialised Palliative Care

Historically hospice use was taken from the Minimum Dataset (MDS) held by the National Council of Palliative Care as used in Hatziandreu et al. (2008) and McBride et al. (2011) which was replaced by the National End of Life Care Intelligence Network (NEoLCIN, 2021).

## Charities

As mentioned in the previous chapter, a considerable amount of funding for end of life care comes from charities. These data are difficult to capture but can be included if the charities themselves provide the data, for example, Marie Curie supplied data in Round et al. (2015).

## 3.3. Routinely collected data for cost analysis - case studies

Next to all reasons outlined in chapter 3.1.1 in order to keep the patient burden at a minimum, especially the potential burden added through conducting research, it can be argued that scrutinizing health care data which are routinely collected is a meaningful starting point. Administrative data can provide meaningful insights into care pathways, has the potential to help understanding potential structural inequities and does not need any of the patient's or caregiver's time.

The following two papers focus on resource use in the last year of patients' lives and connected costs. The papers' aim was to identify cost trajectories in the final year of life, with the objective to understand patient pathways and find patterns of resource use connected to patients' demographics or disease group. After accessing data, the aim needed to be re-adjusted to focus on secondary care only for the Scottish arm of the project as no other data were obtainable.

The first paper presents research outputs across all disease groups whereas the second one narrows down to the cancer population. The cancer project included additional information about the cancer types by merging the cancer specific dataset SMR06 with the existing file. This enabled us to have a closer look on a variety of cancer types and identify predictors of resource use and connected costs. It allowed us to identify cancer specific care needs with the potential of informing decision making processes within the health care system.

Supplementary material to both papers as well as the links to the English papers can be found in Appendix 6.C.1, 6.C.2 and 6.C.3 respectively.

## 3.4. Governance

The use of healthcare data in Scotland is permitted only if public or patient benefit can be demonstrated for the specific use case or project. Scientific peer review of research design is an important part of this process. Prior to commencing the studies described in this chapter, a funding application for the work was submitted to the "Efficiency Research Programme" of the Health Research think-tank "The Health Foundation" in July 2016. This included detailed information about the proposed research, methods, involved organisations, milestones and project management, budget, the research team's expertise, experience and responsibilities. As part of the Health Foundation review process the application was subjected to rigorous scientific and patient peer review.

The subsequent studies needed various datasets in England and Scotland to be linked. In order to facilitate the process, close collaboration with data experts at Imperial College London with the Big Data Analytical Unit and with (BDAU) and with the electronic Data Research and Innovation Services (eDRIS) located at the University of Edinburgh was essential.
Both Units assisted with research governance enabling data access, data linkage and subsequent storage.

In order to access the English data an honorary contract from the Imperial College London was necessary. Despite the application process being time consuming it was well supported by the administrative team in London. In the next step the "Imperial - Information Security Awareness Training" was completed, prior to submitting the "BDAU user registration form". Once all access was granted a short tutorial was provided which helped with navigating the safe haven.

A similar process was needed to access the Scottish data, which linked the Local Authority dataset, NRS Deaths, Prescribing, SMR00 and SMR01. In the follow up study the cancer dataset SMR06 was additionally linked.
In a first step the "MRC - Research Data and Confidentiality e-learning course" needed completion, before registration as a user for eDRIS. Note for future research that a period of three to four months might be necessary from application to gaining final access.

Ethical approval was obtained from the "Imperial College Ethics Committee". In Scotland, a generic NHS ethics approval covers research conducted in the Scottish National Safe Haven operated by Public Health Scotland. A project-specific approval was still needed from the Scottish Public Benefit and Privacy Panel for Health and Social Care (PBPP).

## 3.5. Study 1: Healthcare use and cost trajectories during the last year of life: A national population administrative secondary care data linkage study

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**Abstract**

**Background:** People who are nearing the end of life are high users of healthcare. The cost to providers is high and the value of care is uncertain.

**Objectives:** To describe the pattern, trajectory and drivers of secondary care use and cost by people in Scotland in their last year of life.

**Methods:** Retrospective whole-population secondary care administrative data linkage study of Scottish decedents of 60 years and over between 2012 and 2017 (N=274,048).

**Results:** Secondary care use was high in the last year of life with a sharp rise in inpatient admissions in the last three months. The mean cost was £10,000. Cause of death was associated with differing patterns of healthcare use: dying of cancer was preceded by the greatest number of hospital admissions and dementia the least. Greater age was associated with lower admission rates and cost. There was higher resource use in the urban areas. No difference was observed by deprivation.

**Conclusions:** Hospitalisation near the end of life was least frequent for older people and those living rurally, although length of stay for both groups, when they were admitted, was longer. Research is required to understand if variation in hospitalisation is due to variation in the quantity or quality of end of life care available,

varying community support, patient preferences or an inevitable consequence of disease-specific needs.

**Keywords:** palliative care, end-of-life care, costs, healthcare use, big data, value;

**Background**

Improving the availability and quality of palliative and end of life care is a global priority set out by the WHO in their resolution on palliative care. (Connor, Bermedo, & editors., 2014) In 2015 The Scottish Government published The Strategic Framework for Action for Palliative and End of Life Care, with a vision that '*By 2021, everyone in Scotland who needs palliative care will have access to it*.' (Scottish Government, 2015) Whilst ambitious, the vision was said to be achievable through commitments that included commissioning guidance for health and social care partnerships and research to understand current unmet needs and unwarranted variation in access to care and patient outcomes.

A systematic review of Scotland-based palliative care research published in 2018 revealed a lack of health economic research. (Finucane, et al., 2018) This was a timely observation with growing interest in demonstrating the value of healthcare, from the perspectives of people receiving care, and on the part of service commissioners and providers. Realistic Medicine, a landmark report from Scotland's Chief Medical Officer published in 2015, provided clear expectations of a future healthcare system that offered true value and minimised waste; with 'waste' described from the healthcare recipient's perspective, as interventions that do not add value to their care. (Scottish Government, 2016; Scottish Government, 2015)

People who are nearing the end of life are high users of secondary care services, which is referring to healthcare provided in hospitals including accident and emergency and outpatient departments. Around 50% of people in Scotland currently die in hospital. (Bekelman, et al., 2016; Clark, et al., 2014; NRS, 2020) Hospitalisation may be odds with the expressed preferences of people living with advanced illness. (Mills, Buchanan, Guthrie, Donnan, & Smith, 2019) It may be recommended for some people with complex clinical needs, but may also represent a culture and associated practices of so-called 'over-medicalisation'; whereby hospital-based care and interventions do not offer meaningful benefit to individuals and may even cause harm. (Hughes-Hallet, Craft, Davies, Mackay, & Nielsson, 2011; Earle, et al., 2004) Clark et al studied almost eleven thousand hospital inpatients across twenty-five Scottish hospitals on a single day in March 2010. Almost one third of inpatients were in their last year of life, with one in ten dying during their current hospital admission. (Clark, et al., 2014)

A recent paper by Finucane et al describes trends in place of death in Scotland between 2004-2016. (Finucane, et al., 2019) A key finding was the marked reduction in hospital deaths from 58% to 50.1% during the study period and a corresponding increase in deaths in community settings including care homes. Given population projections of rising numbers of deaths and a higher proportion of deaths being in the elderly, Finucane et al make the case for enhanced community palliative and end of life expertise and provision. (NRS, 2018; Office for National Statistics, 2018)

The Community Health Index (CHI) number is a unique identifier allocated to every Scottish resident offers a unique opportunity for robust population-based data linkage. (ISD Scotland, 2019) It was previously used by Geue et al who used a longitudinal dataset linked to the national inpatient record (SMR01) dataset. The relationship between time-to-death (TTD) and age on healthcare service use and associated costs in 14,860 individuals. (Geue, Lorgelly, Lewsey, Hart, & Briggs, 2015) Both TTD and age were significant predictors for hospital costs in the last three years of life. Furthermore, there was some evidence that socio-economic status, as measured by the Scottish Index of Multiple Deprivation (SIMD), influenced resource use.

A systematic review examining the intensity of end of life care found that the most commonly reported measures for care intensity are hospitalisations, ICU admissions and chemotherapy use. (Luta, et al., 2015; Pasman, Brandt, Deliens, & Francke, 2009; De Roo, et al., 2013)

Understanding the type, intensity of care and variation that people nearing the end of life receive is an important before recommendations can be made to improve access to appropriate palliative care. (Bardsley, Georghiou, Spence, & Billings, 2019) The present study was conducted in parallel with a study of end of life healthcare trajectories and costs for decedents in England during 2010-2017. (Luta, et al., 2020) We describe the rationale for separating the two studies in our Discussion section.

There were three key objectives:

1. To describe secondary healthcare use, trajectory and associated costs over the last year of life for the Scottish population.
2. To describe patterns of healthcare use for disease-specific subpopulations.
3. To investigate associations between demographic characteristics, including age, and secondary healthcare access in the last year of life, in order to highlight possible unwarranted variation.

## Methods

A retrospective population-level data linkage study was undertaken, including all decedents in Scotland in 2012 – 2017, who were over 60 years of age on their date of death. Secondary healthcare use was examined over the last 12 months of life. Deaths under the age of 60 were not included, in order to maintain sufficient underlying disease prevalence for meaningful study.

### Data sources

Data were obtained from Public Health Scotland via the Scottish Research Data Safe Haven. Linkage was established between the Scottish Morbidity Record (SMR) outpatient, inpatient and day case and

the National Records of Scotland (NRS) record of deaths using CHI number as the primary key for linkage. (Mills, Buchanan, Guthrie, Donnan, & Smith, 2019) SMR01 includes episode-based patient records that relate to all acute inpatient and day cases. To reduce measurement error, the SMR01 data were checked for data entry anomalies such as duplicates, overlapping and nested episodes (See Supplementary table 1). SMR00 relates to all outpatients (new and follow-up) in specialties other than Accident & Emergency (A&E) and Genito-Urinary Medicine. In addition, we relied on NRS-deaths data and the SIMD.

**Inclusion and exclusion criteria**

Detailed eligibility criteria are reported in Figure S1 (supplementary material). Major inclusion criteria were:

- Death registered between January 1st 2012 and December 31st 2017
- Age at death ≥60 years
- Healthcare data available for a minimum of 12 months prior to death

Figure S1 describes the data sources and the selection of the study population. The NRS death dataset of participants meeting the eligibility criteria was merged with the outpatient dataset SMR00 and with the inpatient and day case data SMR01. Inpatient and outpatient resource use was excluded if the patient identifier (PID) was missing or if the resource use occurred outside the study period.

**Patient characteristics**

Patient characteristics included gender, age and primary cause of death (one of five ICD-10 categories Cancer, Circulatory, Respiratory, Dementia and other). Comorbidity was estimated using the Charlson Comorbidity Index (CCI). (Sundararajan, et al., 2004) The CCI was based on secondary care coding which entailed a 5 year lookback from the patients first admission, with the limitation that only patients who accessed secondary care during their last year of life had a CCI score. An urban-rural indicator was included, developed by the Rural and Environment Science and Analytical Services Division and the Scottish index of Multiple Deprivation (SIMD). (Scottish Government, 2020)

**Outcome measures**

*Inpatient and Day Care*

Hospital inpatient care in the last year of life was captured as: number of hospital admissions, mean number of bed days per stay and total number of bed days over the 12 month period.

To estimate the cost of inpatient care, the Scottish health service costs (Scottish cost book) was used, mainly R040 (Specialty group costs- Inpatients in all specialties excluding long stays) and R040LS (Specialty group costs- Inpatients in all specialties long stays). Critical care stays are included within mean costs. Day cases were costed using R042 (Specialty group costs- day cases). (ISD Scotland, 2019)

*Outpatient care*

Outpatient data included the number and nature of outpatient appointments per patient in the last year of life. Costs for outpatient appointments were derived from the Scottish health service costs documents R044 (Specialty group costs- consultant outpatients), R045 (Specialty group costs- Nurse led clinics) and R046 (Specialty group costs – Allied Health Professionals). The costs are based on national average unit costs for each service code.

**Statistical Analysis**

Descriptive statistics were used to characterise the study population. Means and standard deviation (SD) were calculated for services and costs. Generalised linear models (GLM) as recommended by Glick et al. (2014) were used to model costs as they are robust to skewed distributions typical for HC data. (Glick, Doshi, Sonnad, & Polsky, 2014) Important predictors are age, gender, primary cause of death, SIMD, an urban-rural indicator and comorbidity. In order to estimate the effect of age, primary cause of death and CCI in isolation including the other predictors as covariates in the GLM. (Hazra, Rudisill, & Gulliford, 2018; Moran, Solomon, Peisach, & Martin, 2007) We also assessed potential interactions between age and gender as well as age and cause of death. Analysis used Stata version 16 (StataCorp, College Station, TX, USA).

**Ethics**

Approval was granted by the Scottish Public Benefit and Privacy panel (Ref: 1617-0100) for analysis within the Scottish National Research Data Safe Haven.

## Results

**Patient characteristics**

A total of 339,963 people died in Scotland between January 1st 2012 and December 31st 2017, of whom 274,048 met the eligibility criteria.

Sixty percent of the decedent population were under 80 years old at death and 54% were female (Table 1). The most common causes of death were circulatory diseases (29.2%) and cancer (27.5%).

Around two thirds of the study population lived in urban areas, around 20% in accessible small towns or accessible rural areas and 10% in small remote towns and remote areas.

*Table 1: Study population and resource use [outpatient and inpatient count and standard deviation, overall length of stay (LOS) within a hospital and average in-hospital time per inpatient stay] in the last year of life*

| | Category | N | % | Inpatient Count | Outpatient Count | LOS | LOS/stay |
|---|---|---|---|---|---|---|---|
| Sex | **Men** | 124,860 | **45.6** | 5.4 (5.1) | 3.6 (5.2) | 33.2 | 7.3 |
| | **Women** | 149,188 | **54.4** | 4.9 (4.7) | 2.8 (4.4) | 34.3 | 8.1 |
| Age | **60-64** | 27,671 | **10.1** | 6.6 (6.6) | 5.2 (6.9) | 30.5 | 5.6 |
| | **65-69** | 34,886 | **12.7** | 6.1 (6.0) | 4.6 (6.0) | 32.1 | 6.1 |
| | **70-74** | 46,032 | **16.8** | 5.5 (5.4) | 3.9 (5.4) | 33.0 | 6.9 |
| | **75-79** | 55,987 | **20.4** | 5.0 (4.6) | 3.0 (4.2) | 34.8 | 7.8 |
| | **80-84** | 54,527 | **19.9** | 4.5 (3.8) | 2.2 (3.2) | 35.6 | 8.7 |
| | **85-89** | 38,899 | **14.2** | 4.0 (3.2) | 1.7 (2.5) | 35.0 | 9.5 |
| | **90+** | 16,046 | **5.9** | 3.6 (3.0) | 1.2 (1.8) | 33.7 | 10.0 |
| Main cause of death | **Circulatory** | 80,064 | **29.2** | 4.5 (4.1) | 2.3 (3.5) | 32.7 | 7.6 |
| | **Cancer** | 75,236 | **27.5** | 6.0 (5.8) | 5.4 (6.4) | 32.6 | 7.2 |
| | **Other** | 57,693 | **21.1** | 4.9 (5.0) | 2.5 (4.2) | 36.2 | 8.3 |
| | **Respiratory** | 38,747 | **14.1** | 5.2 (4.5) | 2.3 (3.3) | 35.3 | 7.4 |
| | **Dementia** | 22,308 | **8.1** | 3.7 (3.1) | 1.2 (1.9) | 32.7 | 9.2 |
| SIMD (from most to least deprived) | **1st** | 60,562 | **22.1** | 5.6 (5.0) | 3.3 (4.6) | 34.7 | 7.1 |
| | **2nd** | 61,351 | **22.4** | 5.2 (5.0) | 3.2 (4.8) | 34.1 | 7.6 |
| | **3rd** | 58,400 | **21.3** | 4.9 (4.6) | 2.9 (4.6) | 32.9 | 7.9 |
| | **4th** | 50,101 | **18.3** | 4.9 (4.7) | 3.0 (4.7) | 33.1 | 8.0 |
| | **5th** | 42,982 | **15.7** | 5.1 (5.4) | 3.3 (5.1) | 33.9 | 8.2 |
| Urban/Rural (from Urban to Rural) | Large Urban Areas | 90,172 | **32.9** | 5.6 (5.3) | 3.3 (4.4) | 37.0 | 7.7 |
| | Other Urban Areas | 97,991 | **35.8** | 5.1 (4.9) | 3.2 (5.2) | 32.0 | 7.3 |
| | Accessible Small Towns | 25,904 | **9.5** | 4.9 (4.5) | 3.1 (4.8) | 32.8 | 7.7 |
| | Remote Small Towns | 12,222 | **4.5** | 4.4 (4.7) | 2.4 (3.7) | 33.9 | 9.3 |
| | Accessible Rural | 29,573 | **10.8** | 4.8 (4.7) | 3.1 (4.9) | 31.8 | 7.6 |
| | Remote Rural | 18,186 | **6.6** | 4.4 (4.5) | 2.4 (3.7) | 31.6 | 8.6 |
| Total | | 274,048 | **100.0** | 5.1 (4.9) | 3.1 (4.8) | 33.8 | 7.7 |

**Inpatient, outpatient and day case use and costs**

The mean number of hospital inpatient admissions during the last year of life was 5.1 (SD: 4 9) and hospital outpatient appointments 3.1 (SD: 4.8) (Table 2). The mean total number of hospital bed days in the last year life was 33.8, with a mean length of stay per admission of 7.7 days. Examining the unadjusted differences, males had a higher number of inpatient and outpatient appointments than females but spent fewer total days in hospital due to a shorter average length of stay. Around three-quarters of study participants were hospitalized at least once in their last year, and 29% in their last month of life. Nearly 80% of the study population had one or more outpatient appointment in their last year, with one-third having an outpatient appointment during their last month of life. The number of day case appointments was comparably small with 6.3% of the population having one or more in their last year and just under 0.5% having a day case appointment in the last month of life.

*Table 2: Health Care utilisation in the last year and in the last month of life*

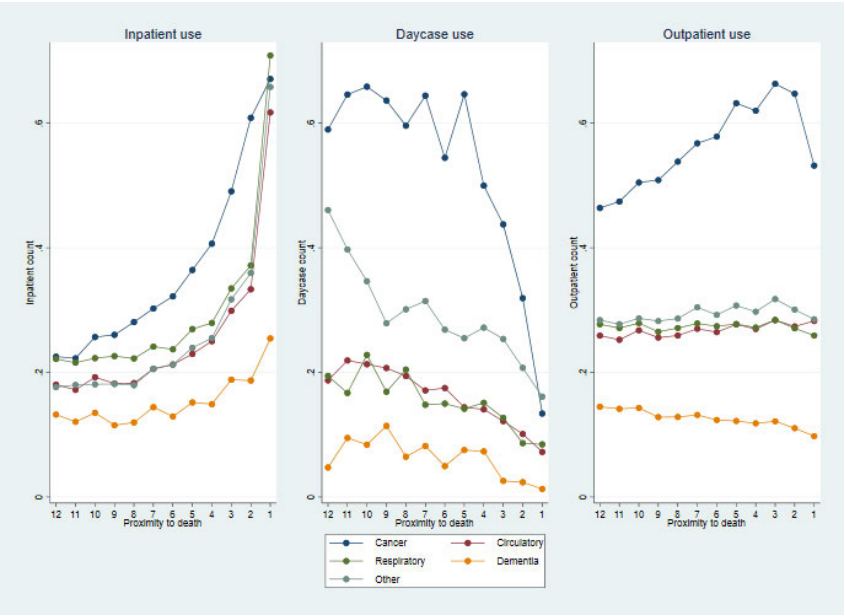
| **Healthcare Utilisation** | N = 274048 | Last 12 month | Last month |
|---|---|---|---|
| **Inpatient care** | Hospitalizations, No.% | 200510 (73.16%) | 80287 (29.296%) |
| | Hospital admissions, mean (SD) | 5.1 (4.9) | 0.856 (1.399) |
| | Hospital duration(days), mean (SD) | 33.8 (37.8) | 5.14 (6.48) |
| **Day cases** | Day cases, No.% | 17540 (6.3%) | 1363 (0.497%) |
| **Outpatient care** | Outpatient visits, No. (%) | 217772 (79.465%) | 92454 (33.736%) |
| | Outpatient visits, mean (SD) | 3.1 (4.8) | 0.406 (0.7007) |

The mean cost of secondary care was £ 10,134 (CI [9,921, 10,337]) per person in the last year of life (Supplementary table S3). Proximity to death had the biggest influence on adjusted monthly costs (Supplementary table S4). The main contributor to costs over the final 12 months of life was inpatient hospital stays; peaking during the last three months when admissions were most common.

**Healthcare use by primary cause of death**

There were significant differences in patterns of healthcare use by decedents' cause of death. (Figure 1). Inpatient hospitalisation rates accelerated over the last year of life for all causes of death, and this was most pronounced in circulatory or respiratory disease. Patients who died from cancer accessed more day care over the last year of life. Frequency of outpatient care remained relatively constant over the last year of life for most groups, except for those who died of cancer were higher users of all three domains of secondary healthcare.

*Figure 1: Resource utilisation (secondary care) in the last year of life for inpatient, day case and outpatient use split by main causes of death*

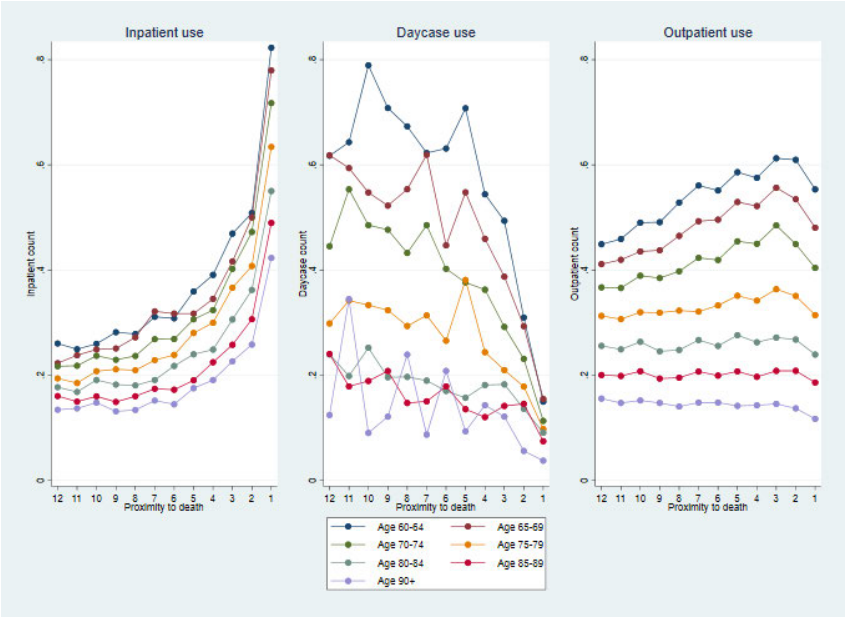



218,357 decedents had an evaluable CCI score, with missing data reflecting those with no hospital records during the last year of life. Around one third of this sub-population had a CCI score of zero, 60% had a score between 1 and 5 and the remaining 5% had a score between 6 and 12 reflecting the highest disease burden (Supplementary table 2). Adding comorbidity as an explanatory variable into a GLM (Supplementary table 3) it can be observed that a higher CCI is associated with higher secondary healthcare costs, but with some variability.

**Healthcare use and costs by age and demographics**

Inpatient hospitalisation increased in frequency in all age categories with proximity to death, with a steep rise in the last three months of life (Figure 2). The frequency of day case use varied considerably over the last year for all age groups, though younger patients accessed significantly more day case care. Outpatient use was largely constant across the last year for the population groups over 75 years of age, whilst the younger population had a slight increase until three months prior to death, followed by a sharp decrease.

*Figure 2: Resource utilisation in the last year of life for inpatient, day case and outpatient use split by age groups.*




One year adjusted and unadjusted costs decreased with increasing age (Table 3 and Figure 2). Unadjusted costs for the youngest group were £12,420.7, which was double the costs for those aged 90 and over. However, after adjusting for gender, primary cause of death, SIMD, RU and comorbidity, costs for the youngest and the oldest begin to converge.

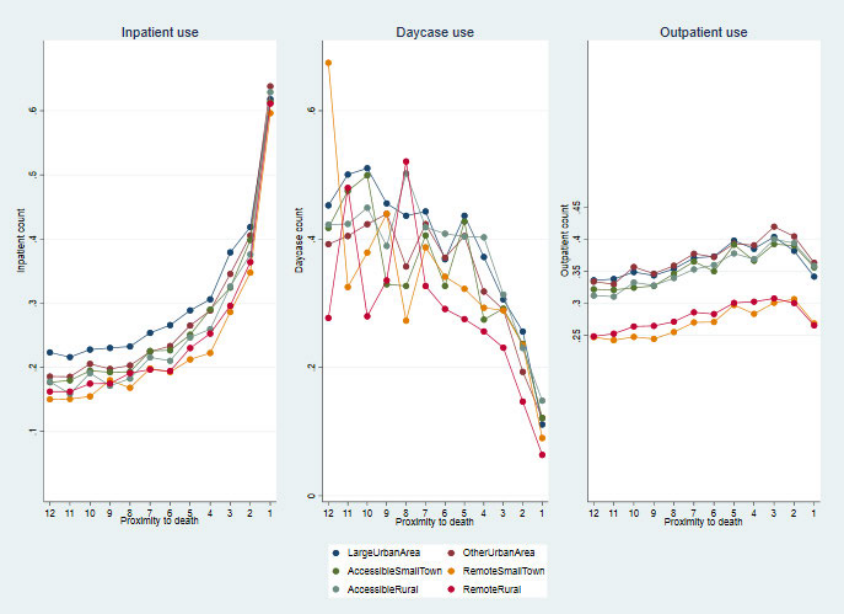
*Table 3: Generalised linear model - unadjusted costs with CIs on the left, adjusted generalised linear model on the right*

| Age group | Unadjusted Costs (£) | CI (95%) | Adjusted Costs (£) | CI (95%) |
|---|---|---|---|---|
| **60-64** | **12420.7**$^{***}$ | [12262.5,12578.9] | **12411.4*****| [12271,12551,9] |
| **65-69** | **11522.1**$^{***}$ | [11391.9,11652.4] | **11894.1*****| [11775.6, 12012.5] |
| **70-74** | **10695.5**$^{***}$ | [10590.5,10800.4] | **11615.5*****| [11515.5, 11715,4] |
| **75-79** | **9525.4**$^{***}$ | [9440.4,9610.3] | **11331.6*****| [11240.7, 11422,5] |
| **80-84** | **8406.5**$^{***}$ | [8330.1,8482.9] | **10970.3*****| [10876.9, 11063.7] |
| **85-89** | **7296.2**$^{***}$ | [7216.6,7375.7] | **10499.6*****| [10388.8, 10610.4] |
| **90+** | **6117.3**$^{***}$ | [6009.0,6225.5] | **10019.3*****| [9843.35, 10195.4] |

| | |
|---|---|
| **Observations** | 260636 |
| Adjusted for gender, main cause of death, SIMD, Urban-rural Indicator, Charlson index | |
| 95% confidence intervals in brackets * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ | |

People living in large urban areas had highest use of all types of healthcare (Figure 3). Those in remote small towns and remote rural areas used fewest resources, with exceptionally low use of outpatient appointments. No clear trend was observed with deprivation presented in Supplementary table 2.

*Figure 3: Resource utilisation in the last year of life for inpatient, day case and outpatient use split by rural-urban indicator*



## Discussion

### Main findings

Inpatient hospitalisation was increasingly common over the last year of life and particularly when close to death. This was consistent across all causes of death, age and rurality groups. On average, people spent more than one of their last 12 months of life in hospital, typically over several admissions. Inpatient costs comprised the greatest proportion of the £10,000 average secondary care cost, at more than £8,500 per decedent.

The intensity and pattern of daycase care and outpatient appointments was more mixed, although the use of both fell sharply close to death with considerably smaller costs, at £400 and £650 respectively.

### Strengths and limitations of the study

The primary strength of our study is that our data covered the entire Scottish population of decedents and captured near-complete secondary care use during their last year of life. Therefore, our resource use estimates are less prone to bias due to non-random selection, as may occur in cohort studies.

The main limitation of our study was the breadth and depth of available data for linkage. We were unable to describe the nature of acute hospital admissions, including reasons for admission and whether the person was admitted to critical care during their inpatient stay. Furthermore, we could not describe the extent to which patients accessed palliative care. These limitations reflect both the lack of usable coded data relating to clinical care episodes, but also, topically, Covid-era restrictions on data access due to human resource reallocation. We must also acknowledge that secondary care represents only one dimension of healthcare. Therefore, data linkage to records reflecting the whole spectrum of health and social care must be a priority for future studies. Our parallel study of decedents in England was able to draw on primary care data, albeit only for a particular cohort. (Luta, et al., 2020)

### What this study adds

Primary cause of death was clearly associated with differing patterns of healthcare use. The population who died of cancer were consistently the most frequent users of secondary healthcare, with those dying of dementia consistently the least, following a pattern previously described by Murray et al. (Murray, Kendall, Boyd, & Sheikh, 2005) Older decedents used significantly less secondary healthcare during their last year of life, as did those living rurally. These results are in line with the findings of our parallel English study by Luta et al (2020).

The extent to which observed patterns of use reflect the needs or preferences of the different populations is unknown. Further research is needed to explore this and to investigate the likelihood of benefit of secondary care interventions close to death. This would allow quantification of the value of care.

Patterns of healthcare use are inevitably influenced by clinical service configuration. For instance, cancer care is predominantly secondary care outpatient-led, with individuals typically receiving treatment as day cases. Therefore, it is not surprising that outpatient and day case use was observed to be particularly high in this subpopulation. Services for people with dementia are more likely to be community or social care-based and it follows that this population access secondary care less than other groups.

The accessibility of healthcare is important, highlighted by our finding that rural populations access lower levels of secondary healthcare during their last year. We do not know whether rural individuals access more primary care or indeed whether their needs differ from those in more urban areas. The parallel study of decedents in England showed that lower frequency hospitalisations in the last year of life for people in the South-West region were accompanied by a greater number of primary care contacts. Luta et al were not able to comment on causation, but it is possible that more primary care support for people with advanced illness may reduce the need for inpatient hospitalisation.

**Conclusion**

Improving the quality and appropriateness of care for people in the last phase of life is a national and international priority.[1,2,5] We have described patterns of secondary healthcare use and associated costs for over a quarter of a million Scottish decedents; highlighting that inpatient hospitalisation accounts for a great proportion of costs, and is of uncertain value.

Detailed prospective quantitative and qualitative exploration around the value of admissions, day care and outpatient visits in the last year of life is needed. Apart from insight into the patient experience and appropriateness of care, this could identify gaps in care and inequalities.

We require better insight into the value of the social care system and how community care can be a realistic alternative to hospital-based care. (Werblow, Felder, & Zweifel, 2007) Integrated health and social care in Scotland is a new reality and provides opportunity for whole system learning. (Scottish Government, 2015)

Ultimately, our goal must be to maximise value all round, with people nearing the end of life receiving high value care that is tailored to their needs, but simultaneously offers value to care commissioners and providers.

**Supplementary material: 3 Figures, 4 Tables**

**Acknowledgements:**

The authors acknowledge the support of the Electronic Data Research and Innovation Service (eDRIS) team (Public Health Scotland) for their involvement in obtaining approvals, provisioning and linking data and the use of the secure analytical platform within the National Safe Haven. Further the authors would like to thank all members of the scientific advisory board namely: Julia Riley, Sandra Campbell, Catherine Urch, Bee Wee, Harry Quilter-Pinner, Ivor Williams and Gianluca Fontana for their valuable input.

**Authorship**

JM and PH led the conception and design of the study. KD led the data acquisition, conducted data management and analysis supported by XL, EG, JM and PH. KD and EG led the data interpretation supported by XL, JB, EL, JM and PH. KD drafted and revised the article supported by JB and PH. All authors critically reviewed and edited the paper and approved the final version to be published.

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**Data sharing**

Data are not available for sharing via application to the Scottish Public Benefits and Privacy Panel.

**Competing Interest**

Competing Interest: None declared.

**Patient consent**

Not required

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Licence for Publication**

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## 3.6. Objectives for a follow-up study

The previous paper presented patterns of secondary care use in the last year of life across different disease groups, namely circulatory diseases, respiratory diseases, dementia and cancer. It showed besides other outcomes, that a major factor explaining the differences in resource-use is the disease group itself.

Cancer patients stood out with high costs and particularly high inpatient care needs, with a steep increase in resource use in the last three month prior to death. It was argued within the research team, that cancer patients in themselves are likely to show vastly different patterns of resource use linked to the "aggressiveness" of the cancer and connected treatment options as well as to the clinical service configuration (mainly inpatient, outpatient and/or primary care based treatment strategy).
In order to explore the differences in resource use within the cancer cohort we applied to gain access to the cancer registry data. Prior to gaining data access, we developed a research plan including feedback from the existing study team and sent an amendment to the Public Benefit and Privacy Panel for Health and Social Care short PBPP for approval.
As the cancer registry data SMR06 is equipped with the same unique patient identifier included in the linked dataset created for the previous study, the datasets needed no formal linkage through eDRIS, but were just merged.

Using the new data, we aimed to gain better insight into the use of secondary health care and connected drivers of costs in the final year of life across the cancer population.

The subsequent paper is focused on the variation between cancer types and the influence of age and multimorbidity on resource use patterns.

## 3.7. Study 2: Variation in hospital cost trajectories at the end of life by age, multimorbidity and cancer type

*Authors: Katharina Diernberger, Xhyljeta Luta, Joanna Bowden, Joanne Droney, Elizabeth Lemmon, Giovanni Tramonti, Bethany Shinkins, Ewan Gray, Joachim Marti, Peter S Hall*

**Abstract**

**Background:** Approximately thirty thousand people in Scotland are diagnosed with cancer annually, of whom a third live less than one year. The timing, nature and value of hospital-based healthcare for patients with advanced cancer are not well understood. The study's aim was to describe the timing and nature of hospital-based healthcare use and associated costs in the last year of life for patients with a cancer diagnosis.

**Methods:** We undertook a Scottish population-wide administrative data linkage study of hospital-based healthcare use for individuals with a cancer diagnosis, who died aged 60 and over between 2012 and 2017. Hospital admissions and length of stay (LOS), as well as the number and nature of outpatient and day case appointments were analysed. Generalised linear models were used to adjust costs for age, gender, socioeconomic deprivation status, rural-urban (RU) status and comorbidity.

**Results:** The study included 85,732 decedents with a cancer diagnosis. For 64,553 (75.3%) of them, cancer was the primary cause of death. Mean age at death was 80.01 (SD 8.15) years. The mean number of inpatient stays in the last year of life was 5.88 (SD 5.68), with a mean LOS of 7 days. Admission rates rose sharply in the last month of life. One year adjusted and unadjusted costs decreased with increasing age. A higher comorbidity burden was associated with higher costs. Major cost

differences were present between cancer types.

**Conclusions:** People in Scotland in their last year of life with cancer are high users of secondary care. Hospitalisation accounts for a high proportion of costs, particularly in the last month of life. Further research is needed to examine triggers for hospitalisations and to identify influenceable reasons for unwarranted variation in hospital use among different cancer cohorts.

**Keywords:** healthcare use, end of life care, secondary care, costs, cancer;

Approximately thirty thousand people in Scotland are diagnosed with cancer each year, of whom 10,000 live less than one year. [1] It is estimated that two out of five people will develop cancer in their lifetime. Over the last decade, cancer incidence has risen in Scotland, whilst the mortality rate has fallen. This trend can be explained by improvements in diagnosis and the development of newer anti-cancer therapies, the ageing population and the fact that cancer incidence increases with age. [2]

In 2018 there were 16,153 cancer deaths registered in Scotland, excluding non-melanoma skin cancers. [3] A quarter of all deaths from cancer (n=3,980) were attributed to lung cancer, followed by colorectal (n=1,743), breast (n=1,001), prostate (n=923), and oesophageal (n=873) cancers. These five cancer types were responsible for more than half of the Scottish cancer deaths.

People who are nearing the end of life are high users of secondary care services. [4] Currently around 50% of people in Scotland die in hospital. [5, 6, 7] A recent paper describing trends in place of death in Scotland between 2004 and 2016, found a reduction in hospital deaths from 58% to 50.1%, during the study period along with a corresponding increase in deaths in community settings including care homes. [8] Within the cancer population, a reduction in hospital deaths was observed between 2009 and 2016, with the percentage of deaths falling from 49% to 41%. [3]

Hospitalisation of patients in the last year of life may be recommended and necessary for some people with complex clinical needs and increasing proximity to death. Nevertheless, evidence suggests that clinical interventions close to the end of life may also represent a clinical culture of 'over-medicalisation', with limited or no meaningful benefit to individuals. [8, 9, 10] The 'Realistic Medicine' report by the Scottish Chief Medical Officer recommends aligning clinical intervention with individual patients' needs and preferences and moving away from the historic 'doctor knows best' culture. [11]

The rising costs of cancer treatment, driven by new therapeutic options, is important context and necessitates that the true value of clinical interventions is understood. This is a crucial step ensuring that scarce resources can be directed appropriately. [12, 13]

A systematic review, which included all English language retrospective studies looking at costs in cancer care using administrative data, showed that costs were influenced by a range of sociodemographic, clinical and health system characteristics. Further outcomes presented in the review, reported an exponential cost increase with proximity to death and showed inpatient care as the main driver of this. [14] A systematic review of Scotland-based palliative care research published in 2018 revealed a lack of health economic considerations applied to palliative and end of life matters. [15]

Our recent study of secondary care costs for end of life care included the Scottish population who died between 2012 and 2017. We showed that intensity of healthcare use and costs were highest in cancer patients, mainly due to inpatient stays. [4] Similar results were found in our English parallel study. [16] Furthermore, in both studies the cancer cohort demonstrated a particularly steep cost-increase in the final three months of life, again largely as a result of inpatient hospitalisation.

In the present study, we sought to understand more about the timing and nature of secondary healthcare use and associated costs for patients with cancer in their last year of life in Scotland and to identify factors associated with any variation identified (e.g. between cancer types, multimorbidity, age at death and socioeconomic status).

**Methods**

The study population in this retrospective cohort analysis included everyone with a recorded cancer diagnosis in Scotland who died between 2012 and 2017 and was over 60 years of age on their date of death. Hospital-based healthcare use over the last twelve months of life was examined via the linkage of cancer records (SMR06) to data from Scottish hospital records. The final dataset included cancer registry data, inpatient, outpatient and day-case activity (SMR00 and SMR01) and the National Records of Scotland (NRS) death registration data.

**Ethics and consent**

Approval for the study was obtained from the Scottish Public Benefit and Privacy panel (Ref: 1617-0100) for analysis within the Scottish National Research Data Safe Haven.

**Data sources**

Data were obtained via the Scottish Research Data Safe Haven from Public Health Scotland, who manage all health related data connected to NHS Scotland. Linkage was established using the Community Health Index (CHI) number as the primary key. [17] The Scottish Morbidity Record (SMR) outpatient (SMR00), inpatient and day case (SMR01) and the National Records of Scotland (NRS) record of deaths were linked to cancer registry data (SMR06). SMR01 includes episode-based patient records that relate to all acute inpatient and day cases. SMR00 relates to all outpatient activity including new and follow-up appointments. NRS manages the official register for deaths in Scotland, which includes all deaths with details on causes of death from a death certificate. All patient identifiers including the CHI were removed from the datasets prior to release in the National Safe Haven. Data quality control followed the well-established internal protocols of Public Health Scotland, undertaken prior to receiving the anonymised research extract.

**Inclusion and exclusion criteria**

Data linkage and detailed eligibility criteria are reported in Figure S1 (supplementary material). Major inclusion criteria were:

- Death registered between January 1st 2012 and December 31st 2017
- Age at death ≥60 years
- Healthcare data available for a minimum of 365 days prior to death
- A linked record available in the cancer registry between January 1st 2011 and December 31st 2017

In the selection process of the study population, the NRS death dataset of the eligible cohort of decedents was merged with the outpatient (SMR00) and the inpatient and day-case (SMR01) dataset. Inpatient and outpatient resource-use data was excluded if resource use occurred outside the study period. Following this,

SMR06 data was merged onto the existing clean dataset and decedents who did not have a cancer diagnosis were excluded. Data of decedents with a cancer diagnosis, fulfilling all other criteria for inclusion, were retained for the final analysis.

**Patient characteristics**

Patient characteristics included gender, age and primary cause of death, with a subsequent division into cancer as the primary cause of death and an "others" category. Cancer types were grouped based on number of patients and/or using the first two digits of the ICD-10 code. Comorbidity was estimated using the Charlson Comorbidity Index (CCI), based on secondary care coding, which entailed a 5 year look back from patients' first contacts with secondary care using ICD-10 code lists developed by Public Health Scotland. [18] A rural-urban indicator was included, as was the Scottish Index of Multiple Deprivation (SIMD). [19, 20]

**Outcome measures**

*Inpatient and Day Care*

Hospital inpatient care in the last year of life was captured as the number of hospital admissions, the timing of these in relation to death, the mean number of bed days per inpatient stay and the total number of bed days over the twelve-month period.

Scottish health service costs (Scottish cost book) were used to estimate the cost of inpatient care, mainly specialty group costs including inpatient data for: (i) all specialties excluding long stays (code R040), (ii) long stay specialties (R040LS), and (iii) specialty group costs for day cases (R042). [21] Costs related to critical care stays were included within the specialty group costs (i) and (ii). Scottish health service costs include all direct and indirect costs for each care episode within a specific specialty. Direct costs include all bed days, theatre hours, staff (medical, nursing, and pharmacy), therapy (radio-, physio and occupational), laboratory charges and others. Indirect costs include administration, catering, uniforms, laundry, waste disposal, heat, light, power, rent, furniture and more.

*Outpatient care*

Hospital outpatient data included the number of outpatient visits per patient in their last year of life, as well as the reasons for each individual appointment. Costs for outpatient appointments were derived from the Scottish health service costs documents for; (i) specialty group costs for consultant led outpatient appointments (R044), (ii) specialty group costs for nurse led clinics (R045) and (iii) specialty group costs for Allied Health Professionals services (R046). The costs were based on national average unit costs for each service code.

**Statistical Analysis**

Descriptive statistics were used to characterise the study population. Means and standard deviations (SD) were calculated for service use and costs. Aggregated results and results split by cancer type are presented. Gamma generalised linear models (GLM) with log-link, as recommended by Glick et al. (2014) were used to model costs as they are robust to the skewed distributions and the heteroscedasticity typical for healthcare related cost data. Known important predictors of costs are age, gender, primary cause of death, deprivation, urban-rural indicator and comorbidity. [22, 23, 24] The effects of age, primary cause of death and CCI were estimated in isolation, with the other predictors included as covariates in the GLM. Potential interactions between age and gender and between age and cause of death were also assessed. Analysis was carried out using Stata version 16 (StataCorp, College Station, TX, USA).

**Results**

***Patient characteristics***

Table 1 displays the patient characteristics for the final cohort comprising 85,732 decedents with a cancer diagnosis. Slightly over half of the study population was male (52.24%). The greatest proportion of decedents were aged between 70 and 79 years at time of death. The most common cancer type as a primary cause of death was lung cancer, making up over 20% of the included population.

*Table 1: Descriptive characteristics of Scottish decedents (2012 to 2017) with a cancer diagnosis*

| | Frequency | Percent |
|---|---|---|
| Sex | | |
| Male | 44787 | 52.24 |
| Female | 40945 | 47.76 |
| Age category | | |
| 60-64 | 11937 | 13.92 |
| 65-69 | 14640 | 17.08 |
| 70-74 | 17279 | 20.15 |
| 75-79 | 17594 | 20.52 |
| 80-84 | 14173 | 16.53 |
| 85-89 | 7817 | 9.12 |
| 90+ | 2292 | 2.67 |
| Cancer type/ group | | |
| Cancer not main cause of death | 21179 | 24.70 |
| Bronchus/Lung | 18372 | 21.43 |
| Colon/Rectosigmoideum/Rectum | 6342 | 7.40 |
| Oesophagus/Stomach | 5540 | 6.46 |
| Kidney/Bladder | 3555 | 4.15 |
| Liver/Intrahepatic | 2398 | 2.80 |
| Pancreas | 3334 | 3.89 |
| Haematological | 2342 | 2.73 |
| Brain | 1158 | 1.35 |
| Breast | 2136 | 2.49 |
| Ovary | 1331 | 1.55 |
| Prostate | 2846 | 3.32 |
| "other" cancer | 15199 | 17.73 |
| Charlson Comorbidity Index (CCI) | | |
| CCI 0 or not recorded | 20325 | 23.71 |
| CCI 1- CCI 3 | 53412 | 62.30 |
| CCI 4 - CCI 6 | 5143 | 6.00 |
| CCI 7 - CCI 12 | 6852 | 7.99 |
| Scottish Index of Multiple Deprivation (SIMD) | | |

| | | |
|---|---|---|
| SIMD 1st quintile (Most deprived) | 19393 | 22.64 |
| SIMD 2nd quintile | 19649 | 22.94 |
| SIMD 3rd quintile | 17876 | 20.87 |
| SIMD 4th quintile | 15260 | 17.82 |
| SIMD 5th quintile (Least deprived) | 13462 | 15.72 |
| Urban-rural indicator | | |
| 1 - Large urban area | 37967 | 44.29 |
| 2 - Other Urban Areas | 30263 | 35.30 |
| 3 - Accessible Small Towns | 8194 | 9.56 |
| 4 - Remote Small Towns | 2258 | 2.63 |
| 5 - Accessible Rural Areas | 1288 | 1.50 |
| 6 - Remote Rural Areas | 5762 | 6.72 |
| Percentages have been round to 2.d.p and therefore may not add up to 100% | | |

Cancer was recorded as the primary cause of death in 64,553 (75.3%) patients. Patients who had a cancer diagnosis and died from cancer tended to be younger compared to those with another cause of death. For more details see supplementary Figure 2.

Table 2 presents patient characteristics split by cancer type. The first column presents the cohort of patients who had a cancer diagnosis regardless of the main cause of death. The second column consists solely of those with cancer as the main cause of death. Compared to the whole cohort, patients in this category were slightly younger, from more deprived areas and had a higher level of comorbidity. Despite the study population being limited to older adults (60+), we observed differences in age at death across cancer types, with breast and prostate cancer patients being oldest at their time of death. The highest comorbidity burden was detected in those dying from ovarian cancer. There were noticeable differences in the socioeconomic status (SIMD) of patients by cancer type. Patients who died from lung cancer as their main cause of death were found to have the lowest SIMD with a mean value of 2.53 (1.33) whilst those dying from ovarian-, prostate-, brain- or hematologic cancers were typically less socioeconomically deprived, with a mean SIMD category value of 3 or more, indicating less deprived areas.

*Table 2: Average age at death, comorbidity burden (measured using the Charlson Comorbidity Index [CCI]) and socioeconomic status (measured using the Scottish Index of Multiple Deprivation [SIMD]) of Scottish decedents (2012 to 2017) with a cancer diagnosis presented by cancer type*

| | *All* | *Cancer* | *Bron./ Lung* | *Col/Rec* | *Esoph/ Sto.* | *Liver/ Intr.* | *Pancreas* | *Kidney/Bl.* | *Breast* | *Ovary* | *Prostate* | *Brain* | *Hematolo* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) | Mean (sd) |
| *age death* | 80.01 (8.15) | 78.85 (7.82) | 77.32 (7.35) | 80.15 (7.86) | 78.56 (7.76) | 78.20 (7.48) | 77.99 (7.67) | 80.01 (7.67) | 81.16 (8.57) | 78.61 (7.78) | 80.87 (7.84) | 75.61 (6.89) | 79.66 (7.57) |
| *CCI* | 2.42 (2.17) | 2.70 (2.24) | 2.66 (2.16) | 2.76 (2.28) | 2.39 (1.55) | 2.61 (1.92) | 2.39 (1.79) | 2.66 (2.22) | 3.39 (2.93) | 3.56 (2.87) | 3.01 (2.71) | 2.16 (1.30) | 2.02 (1.34) |
| *SIMD* | 2.81 (1.38) | 2.79 (1.38) | 2.53 (1.33) | 2.93 (1.39) | 2.83 (1.38) | 2.81 (1.41) | 2.95 (1.38) | 2.84 (1.37) | 2.96 (1.38) | 3.00 (1.40) | 3.04 (1.38) | 3.11 (1.36) | 3.05 (1.38) |

Bron./Lung: Bronchus and Lung cancer; Col/Rec: Colon, Rectosigmoideum and Rectum cancer; Esoph/Sto.: Esophagus/Stomach; Liver/Intr.: Liver and Intrahepatic cancer; Kidney/Bl.: Kidney and Bladder cancer; Hematolo.: Hematologic cancer; CCI: Charlson Comorbidity Index; SIMD: Scottish Index of Multiple Deprivation

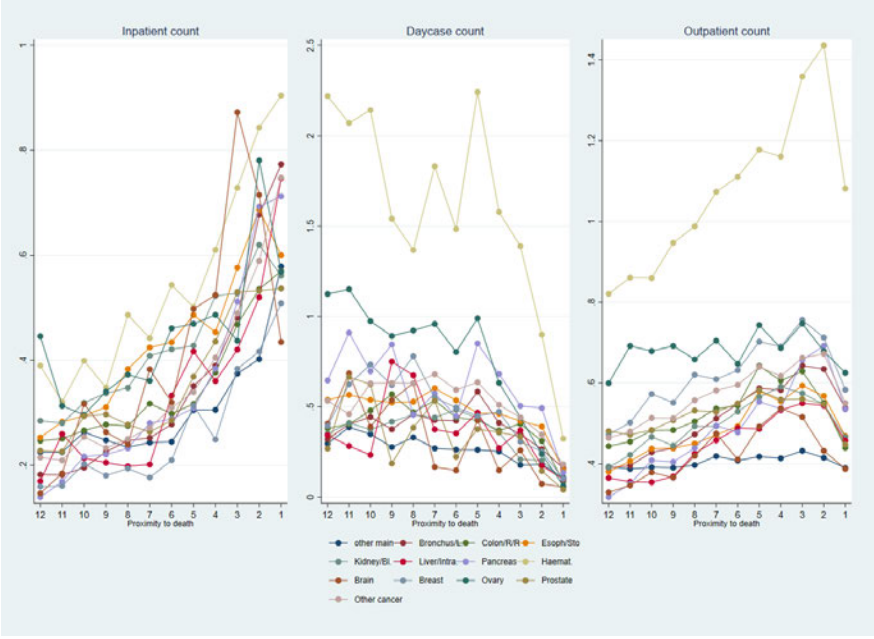
**Inpatient, outpatient and day case use**

Of the 85,732 patients included in the final analysis, 78,919 (92.05%) patients had at least one inpatient stay or day case activity during their last year of life, whilst 75,863 (88.49%) had at least one outpatient attendance. The number of patients with no in- or outpatient appointment was less than 0.1%. The average number of inpatient stays, length of stay per inpatient stay, number of outpatient and day case appointments are presented in Supplementary Table 1. Results are split into cancer types and presented with regards to proximity to death. Over the last year of life, patients with haematological cancers had the most inpatient appointments, with an average of 11.8 stays; but with a comparably shorter mean length of stay (LOS) of 6.1 days per stay. The longest average LOS was recorded for brain cancer patients followed by prostate cancer patients, with 9.07 and 7.94 days per stay, respectively. Haematological cancer patients had the highest number of outpatient appointments in their last year of life (mean 9 9 appointments), followed by ovary and breast cancer patients, with 6.6 and 6.3 appointments respectively. Relatively low resource use was captured for day cases, with haematological and ovarian cancer patients being most frequent day case attenders.

***Patterns of healthcare use and associated costs by cancer type***

Figure 1 demonstrates significant variation in patterns of healthcare use across cancer types. Inpatient hospitalisation rates increased with proximity to death for all cancer types, though at very different rates. Varying degrees of use were observed between patients with cancer as the main cause of death and those who died from other causes, with the latter utilising fewer resources in their last year of life in all three categories (inpatient, outpatient and day case use). Once again, different patterns emerged depending on cancer type. Patients with haematological cancers were consistently high users of secondary care, with associated high costs. Considering the solid tumours only, ovarian cancer patients accessed considerably more outpatient and day care over the last year of life. Patients with certain other cancer types, for example those with brain cancer, recorded a high use of inpatient care whilst other resource use remained low. Conversely, patients with other types of cancer, such as cancers of the lower gastrointestinal tract, showed a high frequency of outpatient use whilst their use of inpatient services was minimal. Overall, frequency of outpatient care remained relatively constant over the last year of life for most cancer groups, except for those who died from haematological cancers. This patient cohort showed a steep increase in outpatient use up to the last month prior to death, followed by a sizeable drop in the last month prior to death. When comparing resource use patterns of decedents with a cancer diagnosis who died from any other cause to those with cancer as their identified main cause of death, higher resource use can be observed for the latter across inpatient, outpatient and day case activity. Whilst patterns were similar for inpatient use with a steep increase especially in the last three month of life, day case and outpatient activity were more frequently recorded in those dying from cancer. For more information, see Supplementary table 3.

*Figure 1: Inpatient, day case and outpatient resource use patterns, in cancer- patients' last 12 months of life. Proximity to death (in month) on the x-axis; average resource use within each month (counts) on the y-axis. Results are presented for each cancer type.*




Other main: cancer not main cause of death; Bronchus/L: Bronchus and Lung cancer; Colon/R/R: Colon, Rectosigmoideum and Rectum cancer; Esoph/Sto.: Esophagus/Stomach; Liver/Intra.: Liver and Intrahepatic cancer; Kidney/Bl.: Kidney and Bladder cancer; Hemat.: Hematologic cancer

The results showing the frequency (presented in absolute numbers) of resource use are in line with the corresponding costs shown in Table 4 (and Supplementary Graph 4) which confirms the outlier position of haematological cancers in terms of costs. Costs for inpatient stays in the last year of life followed a clear and consistent pattern across all cancer types, with a steep rise over the last three months of life.

**Univariate Analysis and Multivariate Analysis**

Results from the univariate analysis (Supplementary Tables 2 to 7) reveal significantly lower costs associated with increased age, female gender and residing in the 3rd and 4th SIMD decile categories (some of the less deprived postcode areas). Costs were observed to be slightly higher for those in SIMD quintile five (least deprived category) and for those living in the most urban areas. However, the majority of the variation in costs was explained by the clinical profiles of decedents, age and their level of comorbidity.

Results of the multivariate analysis (including the sum of inpatient, outpatient and day case costs) (Table 3) confirmed the univariate results with the exception of the SIMD indicator, where only the findings related to the fifth quintile remained statistically significant. This may be due to its correlation with the rural-urban indicator. Adding in an interaction term between age and comorbidity in an attempt to unpick the effects and split the population by cause of death, it was observed that for decedents for whom cancer was the main cause of death, age and comorbidity burden had a bigger impact on costs. (Supplementary Tables 8 and 9)

*Table 3: Generalised linear model – multivariate Analysis, for patients with cancer as a primary cause of death*

| Category | Coefficient | CI [95%} |
|---|---|---|
| Age category | | |
| 60-64 | 0 | [0,0] |
| 65-69 | -0.0845*** | [-0.108,-0.0613] |
| 70-74 | -0.159*** | [-0.182,-0.137] |
| 75-79 | -0.229*** | [-0.252,-0.207] |
| 80-84 | -0.307*** | [-0.331,-0.283] |
| 85-89 | -0.357*** | [-0.385,-0.328] |
| 90+ | -0.396*** | [-0.441,-0.352] |
| Charlson Comorbidity Index | | |
| CCI 0 or not recorded | 0 | [0,0] |
| CCI 1- CCI 3 | 0.661*** | [0.645,0.677] |
| CCI 4 - CCI 6 | 0.649*** | [0.617,0.677] |
| CCI 7 - CCI 12 | 0.909*** | [0.881,0.936] |
| Sex | | |
| Male | 0 | [0,0] |
| Female | -0.0589*** | [-0.0718,-0.0459] |
| Scottish Index of Multiple Deprivation | | |
| SIMD 1st quintile (Most deprived) | 0 | [0,0] |
| SIMD 2nd quintile | 0.0323 | [-0.0159,0.0224] |
| SIMD 3rd quintile | -0.0193 | [-0.0394,0.000707] |
| SIMD 4th quintile | -0.0194 | [-0.0401,0.0661] |
| SIMD 5th quintile (Least deprived) | 0.0499*** | [0.0237,0.0661] |
| Urban-rural indicator | | |
| 1 - Large urban area | 0 | [0,0] |
| 2 - Other Urban Areas | -0.0454*** | [-0.0601,-0.0308] |
| 3 - Accessible Small Towns | -0.0736*** | [-0.0966,-0.0506] |
| 4 - Remote Small Towns | -0.0879*** | [-0.129,-0.0469] |
| 5 - Accessible Rural Areas | -0.149*** | [-0.203,-0.0755] |
| 6 - Remote Rural Areas | -0.103*** | [-0.130,-0.0755] |
| Constant | 9.069*** | [9.041,9,096] |
| Observations | 60728 | |

95% confidence intervals in brackets
* p < 0.05, ** p < 0.01, *** p < 0.001

**Variation of secondary care use between cancer types (GLM for individual cancers)**

Lung cancer secondary care pathways were associated with the lowest costs in the last year of life, followed by those for people with liver cancer (see Supplementary Table 4). Costs were adjusted for age, gender and comorbidity as well as RU and SIMD. Overall, the results presented in table 4 confirmed the findings for all cancers. It was observed that increasing age was associated with lower costs for all cancer types, albeit that the magnitude of cost reduction with increasing age varied by cancer type. When dying from oesophageal, stomach or brain cancer, the last life year was significantly less costly for women than men. An increased number of comorbidities led to a cost increase. Deprivation and rurality did not have a significant effect on costs of secondary care, with the exception of lung cancer patients where the treatment for those residing in areas that are more rural was shown to be slightly less costly. Looking at the costs in absolute terms, it becomes clear that certain cancer types were significantly more expensive than others. The GLMs for the individual cancer types are available upon request, though their translation into monetary values is presented in Table 4.

**Interaction between age and comorbidity burden**

In univariable and multivariable cost analyses for age and comorbidity, increasing age was associated with lower costs whilst an increasing number of comorbidities was associated with higher costs (Table 3).

Interaction terms between age and comorbidity showed considerable variation in their relationship between the cancer types, although these indicated a general tendency for comorbidities to have less impact on costs at older ages. Based on the negative coefficient on the interaction term, a higher comorbidity burden was associated with increased costs but less so with older age. Results supporting this finding are presented in supplementary table 10 and in the supplementary figures 5 to 7.

*Table 4: Generalised linear model results presented for "cancer not being the main cause of death" and all cancer types in- costs (£)*

| Category | Cancer NOT main cause † | Bronchus/ Lung | Colon/Rectosig/ Rectum | Esophagus/ Stomach | Kidney/ Bladder | Liver/ Intrahepatic | Pancreas | Hematologic | Brain | Breast | Ovary | Prostate | Other cancers |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age category | | | | | | | | | | | | | |
| 60-64 | 12489.7 | 12047.2 | 16924.9 | 15373.8 | 15498.8 | 13103.8 | 14551.3 | 36502.8 | 17527.5 | 14392.3 | 25440.8 | 15915 | 16773 |
| 65-69 | 12160.3** | 11537*** | 14619.7** | 14754 | 15325.6* | 12189.1 | 13206 | 29082.8 | 16538.3 | 15148.2 | 21695.9 | 13341.6 | 14426.7*** |
| 70-74 | 10901.1** | 10607.2*** | 12329.2*** | 12298.7 | 14011.7** | 10270.1** | 10829.2** | 25428.1* | 13991.7 | 11862.5** | 18225 | 12835.1 | 13660.5*** |
| 75-79 | 10782.7*** | 9975.3*** | 11063.3*** | 11253.4 | 12704.5** | 10707.5* | 9178.4** | 21420** | 11066.5 | 10185.3*** | 13266.7** | 12719.5 | 12420.5*** |
| 80-84 | 10027.5*** | 9421.6*** | 9933.5*** | 10570.2 | 11551.1** | 8782.1*** | 8640.3* | 15872.9** | 8598.1* | 8652.7*** | 11729.9* | 10919.5 | 10639*** |
| 85-89 | 8993*** | 9250.1*** | 9562.1** | 9505 | 10501.4** | 8487.3** | 7821.3* | 14211.1** | 9787.5 | 6697.4*** | 10232.9 | 9039.1 | 9666.4*** |
| 90+ | 8373.6*** | 9441.3*** | 8760.2** | 8912.8 | 9132.9** | 7073** | 7554.5 | 11717.7* | 10677.7 | 6010.5** | 8576.4 | 8186.6 | 9133*** |
| Sex | | | | | | | | | | | | | |
| Male | 10926.3 | 10695.9 | 12680.2 | 13137.1 | 13783.7 | 10995.6 | 11282 | 24270.9 | 15424.5 | 12408.5 | NA | 12577.3 | 13599.5 |
| Female | 10171** | 10941.8 | 12133.4 | 11808.5*** | 12778.1* | 10952.6 | 11273.7 | 24425.3 | 13558.5** | 11371.2 | 18065.1 | NA | 12699.8*** |
| Charlson Comorbidity Index | | | | | | | | | | | | | |
| No Comorbidity | 9856.7 | 7242.5 | 8526 | 8068.2 | 9640.1 | 8154.5 | 7683.9 | 15875.9 | 9029.6 | 10458.3 | 9301.8 | 10459 | 12262.5 |
| CCI (1 to 3) | 12846.6*** | 11209.6*** | 12779.3*** | 13017.8*** | 13811.7** | 11121.1** | 11832.1*** | 26158.1 | 15620.2* | 12176.6* | 17195.7 | 12900.6* | 14841.5*** |
| CCI (4 to 6) | 17318.7*** | 12356.9* | 12242.8 | 13913.8* | 16209.1 | 12948.3* | 11170.1 | 27551.2 | 12891.7 | 13698.8 | 11815.6** | 14154.9 | 10405 |
| CCI (7 to 12) | 15971.3* | 15886.2 | 17993* | 16038.6 | 17362.4 | 17133* | 15857.8 | 26107.2** | 16307.7 | 15457.5 | 24681.6 | 17407.8 | 15771.6*** |
| Scottish Index of Multiple Deprivation (SIMD) | | | | | | | | | | | | | |
| 1st (most deprived) | 11082.7 | 10864.9 | 12159.9 | 12906.9 | 14177.9 | 11405.7 | 11180.3 | 23633.3 | 13684.6 | 12077.5 | 18527.3 | 13212.6 | 12576.1 |
| 2nd | 10948.3 | 10885.1 | 12423.7 | 12523.1 | 13267.6* | 10874.3 | 10355.8* | 25618 | 14444.4 | 10492.5 | 18008.7 | 12304.5 | 12813.7 |
| 3rd | 10209*** | 10774.5 | 11944.4 | 12607.1 | 12963.1 | 11166.7 | 10589.8 | 22568 | 14943.2 | 11296.5 | 17754.3 | 12821.4 | 12957.6* |
| 4th | 10190.1*** | 10407.9 | 12879.5* | 12528 | 13044.5 | 10221.8 | 12213.8 | 24531.9 | 15078.7 | 10266.7 | 17673.3 | 11710* | 13205.5* |
| 5th (least deprived) | 10318.6** | 11145.8 | 12810.7 | 12644.2 | 13491.2 | 11066.3 | 12329 | 25243.4 | 14813.9 | 12929.9 | 18376.4 | 12924.9 | 14644.6*** |
| Urban- rural indicator | | | | | | | | | | | | | |
| Large Urban area | 10834.5 | 11302.9 | 12937.8 | 13201.3 | 13815.5 | 11734.7 | 11488.4 | 25046.4 | 15258.6 | 11367.6 | 19223.5 | 12951 | 13335.6 |
| Other Urban Areas | 10658.9 | 10477.4*** | 12384.8 | 12338** | 13053.7** | 10301** | 11137.7 | 24397.1 | 14276.1 | 11715.9 | 17468.1* | 12431.4 | 13177.7 |
| Access. Small Towns | 10552.8* | 10346.3*** | 11255.8*** | 12091.1** | 13226.2 | 10939.4 | 11188.4 | 24969.7 | 15058.8 | 12755.7 | 16053.8* | 12598.9 | 12952.9* |
| Remote Small Towns | 9562.9 | 10728.8* | 12451.2* | 11298* | 12287.6 | 8916.5 | 9634.7* | 20620.8 | 13419.2 | 7955.4** | 14700.6* | 11011.5* | 12273.4 |
| Accessible Rural Areas | 8760.5*** | 10138.2 | 10314.5* | 14156 | 12960 | 9952.1 | 10383 | 16496.9* | 13992.2 | 9834.7 | 20233.4 | 12057.9 | 11289.7* |
| Remote Rural Areas | 9367.6*** | 9998.4*** | 11274.1*** | 11797.5** | 13268.1 | 10079.8 | 11575.8 | 21420.6** | 13291.1 | 9719.8** | 16774.7 | 11793.1 | 12926.1 |
| Observations | 21071 | 18294 | 6297 | 5520 | 3542 | 2393 | 3320 | 2331 | 1154 | 2107 | 1322 | 2837 | 15050 |

* p < 0.05, ** p < 0.01, *** p < 0.001

## Discussion

**Main findings**

There is a pervading myth that the escalating healthcare costs observed in developed nations worldwide are solely attributable to the ageing population. Instead of age, comorbidities and cancer diagnosis were identified as the main drivers of variation in cost at end of life for cancer patients over 65. However, patient age remained an important factor, with reduced costs evident for those who are the very oldest. This study's findings confirm the results of our recent studies, showing that patients with cancer dying at an older age use considerably less health care resources in their last year of life than their younger counterparts. [4, 16]

A 'Realistic Medicine' approach has been proposed as a response to a perception of excessive futile intervention in elderly cancer populations. Whilst previous studies have confirmed lower rates of healthcare utilisation at the end of life for those with conditions such as dementia, our results show a high use of hospital-based care for the cancer population, albeit not for all types of cancer. However, clear interactions between age and tumour type are apparent, likely reflecting differential levels of treatment intensity in cancer types where the balance of harms and benefits may be more in favour of treatment. This might be complicated by differences in the composition or severity of comorbidities in different age groups, which may not be captured by the Charlson Comorbidity Index. Further studies with more detailed exploration of comorbidity data available in routine records are needed to unpick this complex relationship.

Variation in healthcare use between cancer types was most pronounced between those with haematological cancers compared with solid tumours. Within the group of patients who had solid tumours, those with ovarian cancer had the highest secondary care use and costs; an observation potentially explained by a practice of patients with advanced disease commonly receiving systemic treatment because of high response rates. This is contrasted with brain cancer decedents who had the lowest secondary care costs; and whose disease may be characterised by low rates of control, cure or response to intervention over the last year of life. It is important to note that this study included decedents only and therefore reflects pathways and outcomes for those who were not cured of their cancer by their treatment.

Alongside the treatment context differences between cancer types, there are many clinical differences in the symptoms and complications that patients experience and the consequences of these for secondary care use. For instance, patients with advanced ovarian cancer commonly experience bowel obstruction or require ascites to be drained, necessitating inpatient admission. Individuals with haematological cancers typically require regular blood product support alongside their treatment, also necessitating in- and/or outpatient care. Therefore, the cancer type and its clinical manifestations, as well as the typical treatment approaches, will necessarily inform the need for secondary care interventions.

Whilst acknowledging the valuable role that hospital-based care offers many patients with cancer in their last year of life, it is also important to consider that some secondary care interventions may not be beneficial. Perceived 'over-medicalisation' towards the end of life has been shown to have a negative impact on patients' and relatives' satisfaction with care and to be linked with a lower quality of life. [25, 26, 27] There is a clear need to elicit patient and family expectations and preferences for care and to aim for a meaningful

shared decision-making approach [11], arguably at all stages of the cancer journey, but especially as the illness advances and the likelihood of benefit from acute medical care may be diminishing.

Alongside the need to align care with patients' needs and preferences, it is also critical that only those treatments and interventions that offer a reasonable chance of benefit are offered, in order that our scarce health care resources are utilised efficiently. New, highly effective treatments for several cancer types have been very welcome, but we cannot ignore the additional financial burden of these on our already strained health care system. It is therefore ever more crucial to ensure that treatments are targeted to those who stand to benefit the most. [12, 13] As costs at the end of life are frequently included in health economic models of new cancer drugs for reimbursement submissions, this study provides data that will be of direct use for this purpose. Furthermore, improving the quality and appropriateness of care for patients in the last phase of life is a national and international priority. [28]

This study confirms recent research showing that secondary care costs typically rise steeply in the last months of life. [4, 29, 32, 33] These are important findings given that the majority of cancer deaths occur in hospital, despite expressed preferences ahead of time by the majority for end-of-life care at home. [30] Likelihood of dying in in-patient palliative or end-of-life care facilities are further dependent on the level of remoteness, with a higher chance of dying in an inpatient facility when driving time is less than ten minutes. [34] A recent trend for more community-based deaths of people with cancer has been observed, and this may reflect an increasing tendency towards advance care planning. An interesting finding in our study was the association between rurality and lower hospital costs, possibly reflecting proactive primary care for more rural populations, and alternative pathways to acute hospitalisation such as community hospital admission. Further lower costs for patients from rural areas could be associated to longer travel times and/or lower access to secondary care; considerations, which need to be taken into account when considering centralising specialist cancer care. [35] Another factor potentially influencing the level of secondary care use is the level of rurality; it was shown to influence cancer related self-efficacy, with an increase in self-efficacy in rural areas. [36]

**Strengths and limitations of the study**

This study captures healthcare data for the entire Scottish decedent population. By including routine datasets covering the whole population, there was low risk of sampling errors and selection bias along with the inclusion of exact incidence and prevalence rates. Furthermore, the administrative datasets covered several years, supporting the inclusion of data from up to five years prior to death (informed the calculation of CCI) as well as decedents over several years. In addition, learning from routine electronic health and administrative records carried no burden for the study participants.

Although the breadth and depth of Scottish administrative data was a strength, there were some notable gaps in our data. We were restricted to deaths in over 60 year olds due to the availability of data which was part of a wider research programme. All data included originated in secondary care, albeit across inpatient, outpatient and daycase services. Primary care 'in hours' and 'out of hours' data was not available for this project, nor was data relating to social care and specialist palliative care and data on drugs. These are

important parts of the care jigsaw, given that even with frequent hospitalisation, most patients spent most of their last year of life being cared for in the community. Furthermore, it did not allow for comparisons in secondary care use to be drawn between patients with differing degrees of primary care or specialist palliative care input; areas which are of great relevance and interest. A further limitation arose from the way the CCI was derived. CCI values were linked solely to inpatient datasets (92% had at least one inpatient appointment) leaving 8% without a CCI value. The results relating to the CCI therefore might have excluded the 'better managed in the community' or 'relatively healthier' patients with a comorbid condition that did not lead to admission or secondary outpatient care. Further data gaps related to specialist cancer treatments such as chemotherapy or radiotherapy. Despite our data not providing detailed information on specialist cancer treatments, due to the underlying structure of the Scottish Health Service Costs it is highly likely that the costs are reflected in the analysis. [21]

It should be noted that our parallel study in England encompassed primary care data, but only for a small sample of the English national population; thus, neither study has managed complete data capture. [29] Future regional studies may be more likely to achieve in-depth, near whole healthcare system examination. A further limitation of this study is that we did not hear from people with advanced cancer or those close to them about their experiences of healthcare and the extent to which the care they accessed offered them meaningful benefit. Future studies should arguably incorporate a mixed methods approach, whereby routine data provides objective data relating to clinical pathways and costs, and qualitative research alongside illuminates the subjective, lived experience. It is only by examining value from both the health system and personal perspectives that we can expect to make recommendations about how resources can be optimally targeted.

**Conclusions**

We have described patterns of secondary healthcare use and associated costs for all Scottish decedents with a cancer diagnosis who died between 2012 and 2017. Our headline finding is that inpatient hospitalisation accounted for the greatest proportion of costs across all cancer types, and particularly so over the last weeks of life. This end of life phase, when deteriorating health is inevitable, is a time when we might reasonably question the value of inpatient hospital care for many.

We recommend further research to identify enablers of a potential shift from secondary care to community care at the end of life. We do not know if the observed drop-off in in day-case and outpatient activity is replaced by community services such as GP contacts and community palliative care visits, or if it is simply replaced by inpatient hospital activity as people become too frail or sick to attend on an outpatient basis. It is not clear from this study, or indeed in others, whether community services are adequately resourced to meet cancer patients' needs as they deteriorate, or if they are potentially underused. It is likely that there are some cancer types which may be more readily supported in primary care than others. We require better insight into the value of the social care system and how community care can be a realistic alternative to hospital-based care if it is both resourced and accessible. We recommend to replicate this study in other

health systems for additional learning. Integrated health and social care in Scotland is a new reality and provides opportunity for whole system learning. [28] Whether primary care can be seen as a substitute for secondary care or not is the rationale for a planned research project that will delve into primary care and community data. [31]

**Declarations**

**Ethics**

Approval was granted by the Scottish Public Benefit and Privacy panel (Ref: 1617-0100) for analysis within the Scottish National Research Data Safe Haven.

**Conflict of Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Authors' contributions**

KD and led the conception and design of the study supported by PH. KD led the data acquisition, conducted data management and analysis supported by EL, EG, JM and PH. KD led the data interpretation supported by EG, EL, GT XL, JB, EL and PH. KD, EL, GT and JB drafted and revised the article supported PH. All authors critically reviewed and edited the paper and approved the final version to be published.

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## 3.8. Learning outcomes and observations

Starting to work with big data means facing a steep learning curve. The incredible amount of data, which theoretically provides endless research opportunities can feel intimidating, hence it takes some patience to work through the structure. This is exacerbated by the need to overcome organisational hurdles, obstacles to data access, obtain the variables applied for and work within different safe haven environments. Some of the challenges experienced working with routinely collected data with connected limitations to the research outcomes are presented below.

### 3.8.1. Learning outcomes - administrative data studies

The main challenge in both included studies was the fact that data were held within the Scottish Safe Haven eDRIS. Safe havens theoretically are a useful way of accessing data which include identifiable data, such as patient records. They have the potential to provide researchers with an impressive breadth and density of data. However, working within data safe havens comes with a variety of challenges, prerequisites and limitations.

What follows is a non-comprehensive compilation of the challenges faced when working on the studies and details of how these issues where addressed and if possible, resolved.

#### Obtaining access to all data specified

Firstly, the main challenge which resulted in substantial limitations for both of the Scottish studies: not all data requested arrived in time for the planned data analysis or indeed arrived at all. Despite tremendous efforts from the study team in

reminding the safe haven team, including frequent mails, in-person and phone conversations with the coordinators, it remained impossible to gain access to variables providing insight on the patients' locations. This restriction not only necessitated ad hoc changes to the planned data analysis as it was originally aimed to detect potential regional variation, but also impacted the comparability to the English parallel publications (which included a regional variable, thus they were able to show some unwarranted variation).

Another important set of variables we originally applied for, rigorously followed up on, but never gained access to, included all patient medication. Knowing that for some disease groups, especially within certain cancer types, medication is a huge cost driver, it would have been of major interest. The main challenge, as argued by the safe haven coordinator, was that there is not enough space on the safe haven to add medication for a study with this sample size, hence emphasising the limitations regarding computational restrictions mentioned by Bain et al. (1997). Despite considerable efforts from our team, who suggested possible solutions, such as limiting this part of the analysis to a small number of pre-specified drugs, no resolution was achieved.

## Safe haven processes

Most of the difficulties faced when working in the Scottish safe haven (eDRIS) are based around the stringent rules regarding data safety. Compared to the safe haven hosted by the Big Data and Analytical Unit (BDAU) at Imperial College London, eDRIS has some additional layers of data security. There is no doubt that researchers like to see data safety ensured, nevertheless some guidelines and regulations can make everyday work tremendously challenging. Some of the most

frequent happenings and approaches to overcome these challenges are listed below.

**Getting data in and out of the safe haven**

Whilst BDAU allows researchers to decide autonomously whether results are fit for disclosure - enabling a smooth workflow as this allows for timely feedback, making it possible to shape projects as a team - with eDRIS, approval is needed for every table and graph to be disclosed. Filling in the disclosure request in itself is a time-consuming process which is frequently exacerbated by a long turnover period within the safe haven.

The eDRIS team themselves anticipate a two day turnover period. However, more often than not, the time exceeded a week or more, mainly due to reasons of staff availability. Expecting a longer turnover time is also recommended if the request contains a larger number of tables and/or graphs. Apart from being disruptive to the workflow, it was often not possible to get results out in time for meetings - which initially did not allow for team input and quick changes to the project. Once the expectations were adjusted to anticipate a full week, data mostly could be presented at meetings. If not, meetings were shifted.

Getting data into the safe haven can be similarly challenging, as all lines of code must be checked by an assigned eDRIS coordinator. This process was made more efficient by adding detailed descriptions to the code prior to requesting an import.

**Setup period - delayed data arrival**

The setup phase of the studies was slowed down due to a late data arrival, which was not complete at that stage. After the final complete data linkage, the process of accessing data was started. Due to the multi-level security access into the safe haven platform, this turned out to be a rather complex endeavour. Having several layers

of security, allows several options for faulty connections. As soon as one level is not working (and it can be difficult for the end-user to identify which one that is) it is not possible to continue. In the best case, issues could be resolved by a complete re-login, more often it was a matter of several hours or longer, depending of the availability of the assigned eDRIS coordinator and the nature of the problem. It was discovered that the connection was most likely to break down during regular working hours. Whenever possible complex tasks were shifted to off-peak periods.

Overall, IT issues within eDRIS took a considerable time to resolve, as researchers had no direct contact with the IT person but corresponded via the coordinator. In addition to the unplanned occurrences of technical issues, there was frequent save haven maintenance time scheduled. eDRIS took researchers comments on board and now announces these in advance.

**Software availability**

A seemingly small detail which can lead to considerable problems is using different versions of a program in and out of eDRIS. In the above studies the software within eDRIS was a newer version than the one provided by the department. This made it impossible to make small changes such as adapting the captions of a table outside of eDRIS, thus frequently leading to considerable efforts due to the need for going through the disclosure process again. It is recommended for future studies to check the software versions in advance and request updates if needed.

**Deletion of linked data**

A major challenge of working with eDRIS is the fact that the linked dataset will be deleted at the end of the study period with potentially detrimental effects on

the study's reproduceability. Nevertheless data linkage follows the same processes, therefore if needed (and funding is available) data could be made available again.

**Summary remark on working in safe havens**

Having a project spanning two safe havens brings a variety of challenges. Firstly, some variation of the variables collected, a dataset including a sample of the population versus whole population, different variable names for similar variables and a variety of other data related issues. This is complicated by the handling of the unique rules of different countries and different interpretations of the rules to ensure data safety. Straightforward requests, such as sharing codes for data analysis, therefore can involve considerable challenges. The research team's original plan for a paper comparing English and Scottish patients was deemed unrealistic. This realisation was made early on in the project upon discovery of a number of organisational barriers prior to an attempt to align a code in order to be applicable across both datasets.

## Key messages and possible solutions

Although working within safe havens involves some big challenges around data access, linkage and manipulation of the data, it has huge potential for research. The amount of information contained in administrative data is enormous. Exploiting administrative data is a useful way to learn about health care needs across a population and can be a helpful tool in improving society's health outcomes.
The next section contains some general advice on working with administrative data.

- **Informed data request and plan in a lot of puffer time**

  Connecting to researchers who have already worked with the data is recom-

mended, along with getting as much information as possible on the dataset beforehand. Be aware that from the time of the PBPP application which takes time to prepare in itself, it will take several months to obtain approval.

It is difficult to predict how long it takes to finally get access to the requested data and seems sensible to plan for at least half a year. In order to get a better estimate it could be worthwhile to speak to the eDRIS coordinator assigned to the project and consider whether the data have been linked before, as some datasets pose a bigger challenge for linkage than others.

- **Login process and safe haven maintenance**

  Another aspect which might take considerable time is setting up all the processes to be allowed to enter the safe haven. It usually requires a VPN access to the University desktop to access the safe haven, and this in itself consists of a lengthy login process requiring passing several levels of security. If one of the networks needed is faulty, it would be worth trying a few more times before working on something else for the day.

  It is strongly recommended to take notice when safe haven updates are announced or maintenance is scheduled, as during maintenance periods computing is likely to be slow, or the safe haven can be completely inaccessible.

- **Plan in time for data cleaning**

  Get a data dictionary and prepare a code or request a code from other researchers for data cleaning. This is one of the steps that can partially be done before gaining full access.

- **If possible, access training on working with administrative data**

  As it is a rapidly evolving field, more training opportunities are expected to

arise. The ECRUSAD webside is a platform for researchers working with administrative data and provides useful links (eCRUSAD, 2022).

- **Keep the research protocol flexible**

  Despite it not usually being best practice, it might be good advice to have some backup plans and be open to unexpected changes. Working with big data is not yet a fully structured process and there is a high chance to experience some unexpected issues. Being open to protocol changes and having an option to change the focus of the project if not all data arrive in time for the project, could be worthwhile. Check if there is the option to use sub-samples of data which may be easier to obtain than the ones originally requested.

- **Don't be afraid to send reminders**

  ...and get to know the project's eDRIS coordinator. A good working relationship can speed up requests. Do not be afraid to send reminders.

- **Be aware of data limitations**

  Administrative data are not primarily collected for research, therefore some of the variables of interest may not not available. Adapt expectations to what is possible within these data and think about ways to fill in the gaps.

To put it in the words of one of my colleagues: *"Working with administrative data is like learning to tame a dragon — albeit challenging, it is also exciting and rewarding!"* Dr. Lemmon

# Chapter 4

## Estimating resource use and costs - Clinical trials

## 4.1. Capturing resource use & deriving costs in clinical trials

Although routine data can provide substantial insight into resource use and costs at the end-of-life, given the breadth of data, their use is limited when trying to understand causal effects (due to being observational), and is restricted to the data collected (which was not originally for research purposes). As shown in chapter 3, great insights can be gained into some sectors of care, such as in the case of secondary care in Scotland. In the English studies conducted in parallel, some of the primary care data were included but these were limited to GP visits, which was certainly not extensive.

In order to gain insight into all resources used, especially those not part of routinely collected data, or not accessible for research, Randomized Clinical Trials (RCTs) are a good way to expand our knowledge base. As clinical trials are unique and come with the opportunity to adapt the specifications of 'what data' are collected on a case-to-case basis, they are essential for capturing costs which are not routinely collected. This is of particular importance as in Scotland routinely collected data are not (yet) readily available for anything but hospital based care, which is just one care component (setting) when looking at the end of life, despite adding up to a considerable share of costs.

*Note:* Despite primary care data being collected and held by Scottish Primary Care Information Resources (SPIRE), they are mainly used to provide GP practices with resource use information and are not yet fully exploited for research purposes. Further there is an option for patients to opt-out (no whole-population, but sample data), therefore GP patient records are no longer available to Public Health Scotland (PHS, 2022).

What and how much we can learn from a clinical trial in terms of resource use and connected costs is strongly dependent on the trial design. In addition to the differences in trial design, the subsequent examples highlight some variation in a study's potential for producing health economic outcomes; ie for one of them health economics was an integral part from the project start whilst the other showcases some additional challenges as health economic involvement started at a later stage. The following two clinical trials therefore also reflect some of the development in the field of health economics with the trend towards integrating health economics into every stage of the trial (which is now a requirement from many funders).

For detailed information on the contribution to the trials, and a short preview please look at chapter 2.3.

## 4.2. Routinely collected data vs RCTs

Randomized controlled trials come with a different set of benefits and challenges, and outcomes are strongly dependent on the quality of the data collection. Data generated from RCTs are substantially different from those routinely collected, with some of the main reasons detailed below.

### Research question

Huge variation is down to the fact that research based on routinely collected data (administrative data) and RCTs are typically trying to answer different types of question. Hemkens et al. (2016) argue that routinely collected data can cater to: *"almost any research topic and treatment comparison [] of many patient-important clinical events and mortality."*

Nevertheless, research outcomes on new and innovative treatments can not be

observed in routinely collected data, given they are as such deviating from standard care. Hence, insights into resource use within new interventions can just be obtained by collecting data in a trial setting.

## Research outcomes

The study population within RCTs differs from the real-world target population due to two main reasons. Firstly, treatments frequently differ from routine care and secondly inclusion-exclusion criteria apply. Neither of the points is relevant in routinely collected data, however specific outcomes of interest require deviation from routine care. Therefore, external validity is strongly dependent on the quality, setting and limitations of the collection of routine data. These factors have a huge impact on the generalizability of results.

RCTs might struggle to recruit an adequate sample of patients with rare conditions and struggle to include specific demographic populations. Both of these requirements are easily fulfilled in routinely collected data, due to the large populations included and liberal criteria of inclusion. Nevertheless within big data studies, subgroups have a high risk of false positive findings whilst rare conditions suffer from referral biases and are confounded by indication (Hemkens et al., 2016; Hernán and Robins, 2006; Schneeweiss and Avorn, 2005).

Similar issues occur for uncommon outcomes as big datasets may result in some significant and false-positive findings due to overpowered studies. Nevertheless they offer a large number of events due to large populations and long observation periods whilst RCTs often struggle to reach sufficient statistical power.

One main advantage of routine data is the fact that they are panel-data by default,

allowing the observation of development over time, whilst follow-up in RCTs is commonly short, limiting results to the study period or relying on extrapolations.

## Practical considerations

In terms of practical considerations such as e.g. Cost, Speed, Data access, Regulations, Ethical conduct, Conflicts of interest and others, RCTs and routine data studies come with distinct sets of requirements and challenges.

At first glance, the costs of research might be strongly in favour of routine data studies. RCTs obviously have high costs for logistics such as data collection, data generation and database management. Nevertheless, administrative data are expensive, necessitating large investments in data infrastructure, data collection and maintenance of services such as the electronic health records. Research on routinely collected data is expensive due to the cost connected to using save haven services; Both of the applied examples used the safe haven infrastructure coming with at a cost of approximately £15,000. A further difficulty within big data is the lack of standardisation within and across health systems, which is increasing costs and might create false leads.

Similar issues occur with regards to speed. Within clinical trials a lot of time can be needed Hemkens et al. (2016) *for planning, protocol development, regulatory issues, and patient recruitment; time of follow-up until outcomes are observed*. Alternatively, big data are not always as readily available due to issues relating to data governance and linkage.

Data analyses within trials are commonly handled by a single person or a small team, hence creating a higher risk for errors, whilst analysis of routine data frequently involves a number of analysts. It is recommended that trials and administrative data

studies are set up by multidisciplinary teams to improved research plans, include the viewpoints of all stakeholders (especially patients - PBPP) and therefore improve the robustness of the research.

In terms of regulations RCTs and administrative data studies require detailed processes around ethical and regulatory approvals, the latter mainly in connection with data safety. Nevertheless, these processes ensure better oversight and fewer opportunities for error and bias. The requirement for ethical approval in RCTs is crucial; Research with a *"(p)roven disadvantage or anticipated harm with one treatment (lack of equipoise)"* is categorically excluded. In administrative data studies the size and effect of these treatments theoretically can be documented - nevertheless if one treatment is clearly inferior one hopes not to find it in routine care.

With regards to data access Hemkens et al. (2016) argue that data for RCTs are frequently collected by industrial sponsors without access to raw data, making reproduction of the results impossible. Administrative data studies eg the ones included in this work will equally struggle to guarantee reproducability due to eDRIS' regulation necessitating the deletion of the linked datasets.

Due to data regulations it remains difficult to link data collected within a trial to routine data. Health economic analysis alongside clinical trials therefore solely relies on primary data collection.

Further some of the data are collected from specific local areas only and the systems used for collection differ across and within countries ie between NHS Lothian and other Scottish areas. This makes it very hard to link data and explains why it can take years until linked datasets are available.

Overall, routine data and RCTs both come with their own strength and weaknesses and it might be good (future) practice to combine both of them. Studies based on routinely collected data can provide very helpful insights into most questions regarding clinical events; nevertheless in order to capture causalities RCTs are needed. Additional insight on the causalities can be found with the help of qualitative research, which is more frequently a component in RCTs.

The following sections will showcase two trials before discussing insights gained in terms of data collection and analysis of resource use costs.

## 4.3. Trial 1: Does an institutionalised approach to cancer pain assessment and management result in more individualised and cost efficient care?

*Authors: Katharina Diernberger, Eleanor Clausen, Gordon Murray, Bee Wee, Stein Kaasa, Peter Hall* and Marie Fallon*: On behalf of EPAT study group*
**Joint senior authors*

**Abstract**

**Objective:** To understand individual prescribing and associated costs in patients managed with the Edinburgh Pain Assessment and management Tool (EPAT).

**Methods:** The EPAT study was a two-arm parallel group cluster randomised (1:1) trial including 19 UK cancer centres. Study outcome assessments including, pain levels, analgesia, non-pharmacological and anaesthetic interventions, collected at baseline, 3-5 days and if applicable 7-10 days after admission. Costs calculated for inpatient length of stay (LoS), medications and complex pain interventions. Analysis accounted for the clustered nature of the trial design. In this post-hoc analysis, healthcare utilisation and costs are presented descriptively.

**Participants:** 487 patients randomised to EPAT and 453 to Usual Care (UC).

**Main outcome measures:** Pharmacological and non- pharmacological management, complex pain interventions, length of hospital stay and costs related to these outcomes.

**Results:** The mean per patient hospital cost was £3,866 with EPAT and £4,194 with UC, reflecting a mean LoS of 2.9 days and 3.1 days respectively. Costs were lower for non-opioids, NSAIDs and opioids, but slightly higher for adjuvants with EPAT than with UC. The mean per-patient opioid costs were £17.90 (EPAT) and

£25.80 (UC). Mean per-patient costs of all medication were £36 (EPAT) and £40 (UC).

Complex pain intervention costs were £117 with EPAT per-patient and £90 with UC. Overall mean cost per patient was £4018.3 [95% CI 3698.9 - 4337.8] with EPAT and £4323.8 [95% CI 4060.0 - 4587.7] with UC.

**Conclusion:** EPAT facilitated personalised medicine and may result in less opioids, more specific treatments, improved pain outcomes and cost savings.

**KEY MESSAGES**

What was already known?

EPAT resulted in improved pain relief with no increase in opioid related side effects.

*What are the new findings?*

EPAT results in prescription of less opioids but more adjuvant analgesics and non pharmacological approaches. Reduces costs overall.

*What is their significance?*

*A) Clinical*

Consistent simple language and linked algorithms improves pain management, individualises treatment and is cost efficient

*B) Research*

Implementation science methodology is an important next step.

Supplementary material can be found in Appendix 6.D.1.

**Introduction**

Pain is a common symptom among patients with cancer; moderate to severe pain is estimated to affect 38% of patients across all disease stages and 52% of patients with advanced, metastatic, or terminal disease.(1) The sub-optimal management of cancer related pain and subsequent impact on quality of life, functioning, out of hours medical contact and tolerability of cancer treatment is well recognised.(2,3) Simple analgesic strategies in patients with metastatic disease have been shown to lead to good pain control in 85% of patients.(4) However, in the complex environment of modern cancer care, a lack of attention to basic pain assessment and management is common.(5)

We hypothesised that we could improve cancer pain outcomes in cancer centre inpatients by introducing, at institutional level, a simple systematic approach to pain assessment and management using the Edinburgh Pain Assessment and management Tool (EPAT). This new approach is based on strategies to deal with the common clinical shortcomings in cancer care. These include: (a) unstructured assessment; (b) use of treatment guidelines that lack explicit algorithms and do not address clinicians' concerns about prescribing opioids; (c) lack of systematic monitoring of outcomes including adverse effects.(6,7) EPAT facilitates improved assessment with an initial focus on the patient's report of their worst pain, pharmacological management simplified by algorithms, reminder of non-pharmacological approaches and regular reassessment of pain and of drug side effects.

In a study of the effectiveness of EPAT, previously published in The Journal of Clinical Oncology(8), we compared the effect of EPAT (a policy of adding a brief clinician-delivered bedside pain assessment and management tool to usual care [UC]), with that of UC alone, on pain and prescribing outcomes. EPAT achieved better outcomes in both pain and in prescribing practice. In addition, whilst there was no increase in either opioid prescribing nor in opioid related side-effects as a result of EPAT, there was an improvement in how opioids were prescribed.

However, we still need to know (a) whether EPAT leads to the use of more complex interventions and (b) whether it leads to a shift from cheap opioid analgesics to more expensive adjuvant analgesics. The aim of this analysis therefore was to examine the components of pain management in each patient in the EPAT study and the costs incurred by these components.

**Methods**

We used data from the EPAT study, a two-arm parallel group cluster randomised (1:1) trial, in which we recruited consecutive patients on admission with a worst pain score in the last 24 hours of at least 4 out of 10, and observed pain outcomes with UC in 19 UK cancer centres. After the UC phase we then randomised centres to either implement EPAT or to continue UC. The primary outcome was change in the percentage of study participants in each centre with a clinically significant (≥2 point) improvement in 'worst pain' (Brief Pain Inventory Short Form, [BPI-SF]) from admission to 3-5 days after admission. Secondary outcomes included quality of analgesic prescribing and opioid-related side effects.

Ten centres were randomised to EPAT and 9 to UC. We enrolled 1,921 patients and obtained outcome data from 93% (1,795). Participants (mean age 60 years, 49% female) had a variety of cancer types.

***Study assessments***

All study outcome assessments including, BPI, analgesia prescribed, non-pharmacological and anaesthetic interventions, were completed by an independent research nurse at baseline (within 24 hours of admission), 3-5 days after admission and for those who were still an inpatient, at days 7 and 10 after admission. Date of discharge was collected for all patients. Full details of the study can be found in the published paper and in the protocol. (8, 9)

***Delivery of pain management in the study***

The clinicians who delivered pain assessment and management (EPAT or UC) were oncology nurses, general nurses, junior doctors, oncology trainee doctors, and oncologists. In UC centres, the clinical team managed patients according to their existing knowledge, attitudes and local pain guidelines. In EPAT centres, the clinical team was provided with the pain assessment and management tool (Appendix 1) and given brief (30-60 minutes) group training in its use. This training was integrated with the existing educational and update forum structure in each centre.

The training could be very short, as the tool contains no new knowledge, rather it provides a structure and system for the existing general knowledge among professionals working with cancer patients.

***Data on costs***

Costs were calculated for:

a) the length of stay within the hospital (LoS);
b) the medication costs according to the pre-specified frequencies and mode of administration;
c) the intervention costs were calculated for complex pain interventions, such as spinal analgesia, non–pharmacological interventions such as Transcutaneous Electrical Nerve Stimulation (TENS), and palliative radiotherapy for pain.

All costing data, as well as data used for the descriptive statistics, were truncated at day seven in order to stay in line with the original study design. For those patients where the entry date was equal to the discharge date, the day count was set to 0 which meant that their length of stay was 0 days, nevertheless all other costs (medication, intervention) were included in the analysis.

Costs were calculated by the assignment of unit costs to observed resource use and activity. Unit costs were obtained from standard UK NHS reference sources including NHS reference costs as well as Personal Social Services Research Unit cost (PSSRU). Costs were assigned to LoS using a per-diem cost of £745 per day (PSSRU 2018). Units of resource and unit costs are presented in Appendix 2.

**Statistical analysis**

Descriptive statistics split by randomised group (EPAT versus UC) were produced for all complex pain interventions as well as non-pharmacological interventions. Further descriptive statistics show the medication costs categorised in the same way as in the original trial design, namely: non-opioids, weak opioids, strong opioids, adjuvant analgesics, non-steroidal anti-inflammatories and others. As a secondary endpoint, there was no pre-specified statistical comparison of costs between arms and these were therefore not conducted.

All analysis took into account the clustered nature of the trial design. Mean values were first summarised within centres and then the within centre averages were averaged over centres.

Ninety-five percent (95%) confidence intervals around mean costs were calculated by bootstrapping. The preparation of the costs was done in Excel. The main analysis as well as data cleaning were performed using the free and open-source programming language R.

**Results**

Baseline characteristics are similar for the EPAT and UC group for Pain (Worst Pain and BPI-SF) and Distress scores, with a fairly even split between gender in both groups and a mean age of 59.4 and 59.7 years respectively (Table 1).

*Table 1 Participant baseline characteristics*

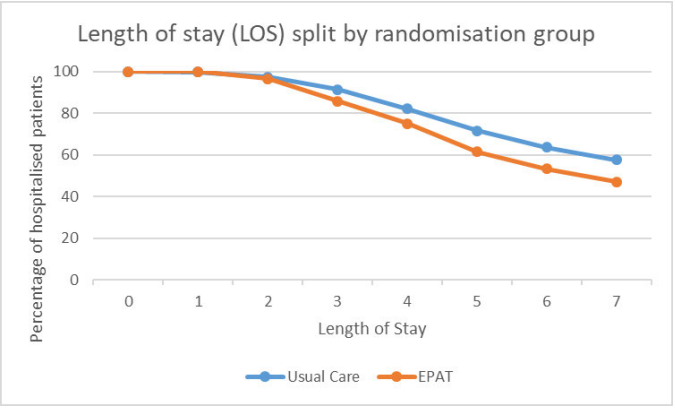
| | | EPAT (487) | | Usual Care (449) | |
|---|---|---|---|---|---|
| **Characteristic** | | Mean | % | Mean | % |
| **Sex** | Female | 240 | 49.3% | 218 | 48.6% |
| | Male | 247 | 50.7% | 231 | 51.4% |
| **Age** | Years | 59.4 | 13.1 (SD) | 59.7 | 13.2 (SD) |
| **Primary cancer** | Breast | 64 | 13.1% | 42 | 9.4% |
| | Genitourinary | 69 | 14.2% | 73 | 16.3% |
| | Gynecologic | 35 | 7.2% | 37 | 8.2% |
| | GI | 69 | 14.2% | 56 | 12.5% |
| | Lung | 49 | 10.1% | 48 | 10.7% |
| | Had and neck | 38 | 7.8% | 45 | 10.0% |
| | Hematologic | 41 | 8.4% | 21 | 4.7% |
| | Other | 115 | 23.6% | 113 | 25.2% |
| | unknown | 5 | 1.0% | 14 | 3.1% |
| **Baseline scores** | Worst pain | 7.8 | 1.8 (SD) | 7.8 | 1.9 (SD) |
| | Global distress | 6.4 | 3.0 (SD) | 6 | 3.2 (SD) |
| | Total BPI-SF | 5.7 | 1.8 (SD) | 5.6 | 1.9 (SD) |

***Length of stay (LoS) split by randomisation group***

At the start of the intervention phase of the study, 487 patients were recruited and randomised into the EPAT group and 453 patients into the UC group at day 0. From day 2 onwards the percentage of patients who were still hospitalised was lower in the EPAT than the UC group (Figure 1).

On the last day included in the analysis 47% in the EPAT group were still in hospital compared to 57% of the patients in the UC group. The mean LoS was 2.9 days in the EPAT group compared with 3.1 in the UC group.

Figure 1: Length of Stay (LoS) split by randomisation group




***Costs for inpatient time (LoS), medication and pain interventions***

The biggest driver of the costs in both arms was the LoS, with an average cost per patient of £3,866 in the EPAT group and £4,194 in the UC group (Table 2). This reflects the results shown in Table 1 where it can be observed that earlier discharge is more likely in the EPAT group.

The medication costs were slightly lower in the EPAT group at £36 per patient compared with £40 per patient in the UC group. The pain specific intervention costs were higher in the EPAT group at £117 compared to £90 in the UC group. These are "one off" procedure costs. Patients in the EPAT group were more likely to receive highly specific, tailored analgesic procedures as seen in Tables 3 and 4.

*Table 2: Per Patient costs for the Length of stay (LoS), Medication and Interventions*

| **COSTS (GBP £)** | **UC (mean)** | **EPAT (mean)** |
|---|---|---|
| LoS | 4193.7 [3954.4 – 4433.0] | 3865.7 [3554.9 – 4176.5] |
| Medication | 40 3 [20.4 – 59.8] | 35 8 [22.3 – 49.3] |
| Intervention | 89 8 [52.2 – 127.4] | 116.7 [54.4 – 179.0] |
| **Total** | 4323.8 [4060.0 – 4587.7] | 4018.3 [3698.9 – 4337.8] |

***Individualised complex pain interventions and non-pharmacological interventions***

Patients assessed by the EPAT tool were more likely to receive complex pain interventions than patients in the usual care group (Table 3). Of note, an external intrathecal line was inserted in 18 patients in the EPAT group, and in only 2 in the UC group.

*Table 3: Complex Pain Interventions by randomisation*

| Timepoint | LNB | CPB | EIT | NPI |
|---|---|---|---|---|
| **Total UC** | 4 | 2 | 3 | 0 |
| **Total EPAT** | 21 | 3 | 28 | 2 |

LNB = Local Nerve Block; CPB = Coeliac Plexus Block; EIT = External intrathecal; NPI =Neurosurgical Pain Interventions

*Table 4: Non-pharmacological Interventions*

| Time point | TENS | Acupuncture | Heat | Cold | CAM |
|---|---|---|---|---|---|
| **Total UC** | 23 | 20 | 149 | 51 | 103 |
| **Total EPAT** | 68 | 33 | 180 | 67 | 79 |

TENS = transcutaneous electrical nerve stimulation; CAM = Complementary and Alternative Medicine

The results from the non-pharmacological interventions follow the same trend, showing that all of the interventions were more commonly used in the EPAT group than the UC group. An example of this is the cheap and simple Trans-electrical Nerve Stimulation (TENS) treatment; this was received by 68 patients in the EPAT group compared to only 23 patients in the UC group.

***Radiotherapy for uncontrolled pain***

Radiotherapy is used as standard management of some types of cancer pain, especially cancer induced bone pain. Table 5 shows that only 30% of patients in the EPAT group required referral for radiotherapy, while 40% of patients in the UC group required referral for radiotherapy.

*Table 5: Radiotherapy count and as percentage of the patients in the control and EPAT group*

| UC | UC% | EPAT | EPAT % |
|---|---|---|---|
| 182 | 40.2 | 148 | 30.4 |

***Medication costs split up into different drug groups***

The mainstay of pharmacological management of cancer pain is based on the following drug groups: non opioids, weak opioids, strong opioids, NSAIDs and adjuvant analgesics. Table 5 shows the costs for these key drug groups of interest in cancer pain split by the EPAT and UC groups. Results are presented as overall costs and broken down into costs per patient. The first three lines show the costs for non-opioids, adjuvants and NSAIDs. Looking at the costs broken down on a patient level for EPAT and UC groups, 487 and 453 respectively, the costs for these non-opioid drugs are small compared to the opioid costs. In the EPAT group there are lower costs for non-opioids and NSAIDs and slightly higher costs for adjuvants compared to the UC group. Looking at the opioid costs it can be seen that the costs for both weak and strong opioids are lower in the EPAT group compared to the UC group, with an overall per patient cost of £17.90 in the EPAT and £25.80 in the UC groups.

*Table 6: Medication costs (in £ sterling) for specific drug groups for control and EPAT group*

| **Drug group** | **UC (total)** | **UC (mean)** | **EPAT (total)** | **EPAT (mean)** |
|---|---|---|---|---|
| Non opioids | 195.1 | 0.4 | 167.8 | 0.3 |
| Adjuvants | 118.9 | 0.2 | 149.6 | 0.3 |
| Non-steroidal anti-inflammatories | 143.8 | 0.3 | 122.6 | 0.2 |
| *Weak opioids* | 265.7 | 0.5 | 148.9 | 0.3 |
| *Strong opioids* | 11456.4 | 25.2 | 8581.4 | 17.6 |
| ***Total Opioids*** | **11722.2** | **25.8** | **8730.4** | **17.9** |

Table 6 shows that the EPAT group are prescribed more adjuvant analgesics but do not have a higher use of any other medication, especially of weak or strong opioids.

There were no regional differences for use of non-pharmacological interventions.

**Discussion**

In the main EPAT study, already published, we demonstrated that improved pain relief was not associated with any excess of opioid related side effects. [8] The aim of this analysis was to examine the components of pain management in each arm of the study and the costs incurred by these components.

This analysis shows that EPAT managed patients received less opioids, but to more adjuvant analgesics, compared to UC. In addition, more non pharmacological treatments, such as TENS machines, were used in the EPAT groups than UC. Similarly, the use of anaesthetic interventional techniques, although small numbers, were more common in the EPAT than the UC groups.
Of interest, fewer patients in the EPAT group required referral for palliative radiotherapy for pain control compared to the UC group.

These components of pain management point to improved pain relief with EPAT as a result of more appropriate individualised management. Adjuvant analgesic prescribing is a very good example of individualised care and implies that the nature of the cancer pain was assessed sufficiently to allow choice of this drug group. In spite of more individualised management, the overall analgesic costs were lower in the EPAT group, driven by less opioid use.

As is often seen in cost analyses, the major driver of costs is length of hospital stay. The EPAT group had a shorter hospital stay than the UC group and this was the major component of overall lower costs in the EPAT group.

In summary, EPAT led to improved pain relief, with less opioid; the opioid reduction was facilitated by more individualised pain management with resultant use of more targeted adjuvant analgesics and non-pharmacological pain interventions. The resultant shortened length of hospital stay drove an overall lower cost with EPAT than with UC.

***Controversies about opioid use***

It is important to discuss EPAT within the context of the significant controversies which have evolved around pain assessment and management.

Many researchers have not been able to demonstrate improved pain treatment or better pain outcome by measuring pain as the 5th vital sign using numerical pain scores.(10-12). As a result there is a movement within the US to abolish pain scores as a surrogate outcome measure of good care, and to stop the exclusive use of unidimensional pain assessment tools, as well as ending the direct

relationship between provider reimbursement and patient self-reports of pain control. (13-19) The Joint Commission, which acts as the regulatory body for many US healthcare institutions, now recognises there is a direct link between healthcare policies, the numerical pain scale, pain expectations and opioid addiction. (18) In the Commission's new guidance it states that "using numerical pain scales (NPS) alone to monitor patients' pain is inadequate" and "stresses the importance of assessing how pain affects function and the ability to make progress towards treatment goals." (19)

The American Medical Association, the American College of Surgeons, The Joint Commission, The American Academy of Family Physicians, and the Centers for Medicare and Medicaid services have all withdrawn their advocacy of the "pain as the 5$^{th}$ vital sign" campaign. Unidimensional self-reported pain scores have been implicated in contributing to the prescribed opioid epidemic and also associated with over-sedation in the acute pain setting. (20)

***Personalised pain control***

The further analyses presented in this paper provide insights into how a brief analytical assessment and linked management tool developed for use in the cancer inpatient setting, is superior to a unidimensional pain rating scale and guidelines. EPAT establishes not just severity of pain, but the characteristics of pain which are then linked with management algorithms. The finding that more individualised and specific management strategies were used might help us to understand how EPAT can improve pain relief with in fact less opioid prescribing.

***Practical implications***

It can be argued that the non-specialist clinician is empowered to prescribe more appropriately by directive assessment and linked algorithms, rather than a simple unidimensional pain scale and broad guidelines which simply suggest drug groups.

Cancer pain can be a complex construct and assessment of its many domains should be conducted using multidimensional tools. Many pain and symptom assessment tools exist for use in the cancer patient, including the Brief Pain Inventory, the McGill Pain Questionnaire, the MD Anderson Symptom Inventory, and the Edmonton Symptom Assessment System, among others. Our challenge is to have an appropriate bedside tool linked to appropriate management for consistent use by non-specialists. (21,22)

***Limitations***

It is important to note that the cost-analysis described in this paper was post-hoc, meaning that it was not pre-planned in the original EPAT trial protocol. Collection of healthcare utilisation was of sufficient depth and quality to make subsequent analysis of high value for decision makers and policy. Comparative cost-analysis is typically characterised by very high variance and skewed distributions, making sample size requirements for statistical comparisons very high and often not feasible in the context of a randomised controlled trial. For this reason our analysis was entirely descriptive and we specifically avoided drawing conclusions of causal inference. Despite this, we believe that the conclusions of the study on the varying distribution of healthcare utilisation and costs between EPAT and UC as valid and likely represent the best achievable level of evidence in this challenging research context.

There are several additional specific limitations of our study one of them was that the focus only on inpatient management and costs. It is possible that earlier discharge may place a greater resource burden on community services. Further research is needed to understand the longer term post-discharge implications of EPAT and to assess the impact of an appropriately adapted community version on pain assessment and management, along with service use. Pain should have an appropriate and accessible common language for professionals, patients and carers and it needs to be consistent across all cancer care settings. The common language of, “pain as the 5$^{th}$ vital sign”, was too simple. We have demonstrated that institutionalisation of assessments appropriate to the clinical setting, linked with appropriate algorithms and reassessment, can both improve pain management with fewer opioids and save money. It is crucial for good patient care and a humane approach to pain, that we do not develop a fear around pain assessment, but rather develop more appropriate ways of assessing and managing pain.

**Conclusion**

An institutional approach to standardise cancer pain assessment and management using EPAT led to less opioid prescribing and improved pain relief without side effects, via more individualised care with specific pharmacological and non-pharmacological management choices. In addition, EPAT also resulted in a cost saving.

These findings support the move away from pain assessment with a unidimensional tool and use of general guidelines and emphasise the importance of an assessment appropriate to the patient group which evaluates aetiology of pain, followed by individualised linked management and reassessment.

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**Conflict of Interest**

None

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## 4.4. Trial 2: A randomized, feasibility trial of an exercise and nutrition-based rehabilitation programme (ENeRgy) in people with cancer

Within the ENeRgy trial, health economic involvement started at the setup and planning phase and was well integrated throughout the whole process. The planned health economic analysis within ENeRgy was published in the trial protocol which can be found in Appendix 6.D.2 section three. Due to ENeRgy being a feasibility trial (with the main goal of observing the data collection and subsequently refining the questionnaire for a potential roll-out) no conclusive health economic analysis plan (HEAP) was developed but rather a short and broad brush description of the planned analysis as described below.

*Estimation of economic parameters will rely on questionnaires designed to measure health-related utility, healthcare related resource use and costs, administered at baseline and follow-up assessment time-points. Missing data will be handled in line with the statistical analysis. Patient reported healthcare utilisation will be assessed for completeness and accuracy by the study team through scrutiny of the patient pathway in both arms of the trial using available patient records. Unit costs will be assigned using standard national costing sources where available, or through consultation with relevant service business managers. Costs will be summarised from the perspectives of (a) the NHS, (b) the charitable and 3rd sector, (c) the patient and their carers and (d) wider society.*

*Funders of large national clinical trials are increasingly demanding evidence that a proposed new intervention has the future potential to prove cost-effective. For this reason a proof-of-concept health economic model will be constructed in accordance with the methodological specification of the NICE Guide to the Methods for Health Technology Assessment. The model will take the form of a probabilistic decision model that simulates the passage of patients through the clinical pathway defined by discrete health states, allowing estimation of costs, quality of life and survival. The model will*

*be parameterised using data from the feasibility trial where possible, supplemented by data from the published literature as necessary. Cost-effectiveness will be presented as the Incremental Cost-effectiveness Ratio (ICER), expressed as cost per QALY gained. Value of Information analysis will be undertaken to aid decision making for funding subsequent research. In light of a prevalent critique of the QALY as a measure of benefit at the end of life, alternative effectiveness metrics will also be presented in line with the secondary clinical endpoints of the study.*

Fulfilling the role as a trial health economist naturally focused involvement on everything related to health economics; the subsequent sections presented detail key steps such as questionnaire development, cost perspective and methods used as well as the health economic results and health economic section of the discussion. Results presented in this work include considerably more detail than the published paper, including the conducted Value of Information Analysis (VOI). The final publication presented a concise summary of the key results in a need to balance reporting on clinical outcomes, health economics and qualitative insights. The publication is included in Appendix 6.D.2 section four.

### 4.4.1. ENeRgy - questionnaire development

In the ENeRgy study, health economics was an integral part throughout the whole project, starting with the study design. This early involvement enabled the creation of a tailored patient questionnaire which was created based on an old version of the "UK Cancer Costs Questionnaire" (which was subsequently updated). It was adapted to an end of life care setting and the particular needs of the trial with the help of clinicians involved in the study. The questionnaire is freely accessible via the DIRUM database (Hall, 2022).

Further, we had input from patient representatives (carers of recently deceased) in study meetings which helped to ensure nothing relevant to patients and the needs

of informal carers was left unconsidered. The health economic questionnaire was integrated into the Case report form (CRF) in the trial.

One of the main goals for developing a questionnaire for the feasibility trial was to assess which questions are of relevance, in order to be able to keep the questionnaire as concise as possible, in a potential larger scale follow up study. The main goal was to make sure all necessary information was captured whilst keeping the burden on patients, family members and health care staff to a minimum.

### 4.4.2. Baseline and follow-up questionnaire

The baseline questionnaires focused on "standard measures" of quality of life such as the EQ-5D-5L and visual analogue scale (VAS) (Herdman et al., 2011; Pickard et al., 2007).
*Note:* It became obvious that these measures are not necessarily the best way of capturing quality of life data in a dying population. Some of the reasons are touched upon in chapter one with the main one being that the domains used in these tools are not well suited to capture the needs of patients at the end of life; secondly no decisive improvement in quality of life nor substantial gains to the remaining length of life were expected.

Nevertheless for the purpose of this work, the focus was on resource use. The only resource use captured at baseline was linked to informal care as the main aim was to capture the support patients got from family, friends and other carers prior to entering the trial.

The follow up questionnaires issued at midpoint and endpoint, weeks 5 and 9 respectively were expanded by adding a conclusive set of questions to capture resource

use. The research team aimed to find an all-encompassing approach to capture all costs directly related to the patients and (informal) carers.

The baseline an follow-up questionnaire can be found in the Appendix 6.D.2 section one and two.

### 4.4.3. Perspective for economic evaluation and cost components included in the health economic section of the CRF

ENeRgy used a combination of a health system perspective and patient perspective for the economic evaluation. Some of the included domains point to a more societal approach and while time off work for patients and carers is captured, this is not a full societal approach as the study did not include a comprehensive spectrum of opportunity costs.

From the patient stories from the introduction, assuming them to be recruited to the study, we can allocate most of the care captured to the following sections in the original UK-Cancer-cost-questionnaire:

- Informal Care: The informal care section remained unchanged; it captured data regarding support from family, friends and other carers
- Hospital care: This section was split into scheduled and unscheduled hospital appointments, inpatient stays and non-physical contact with staff based at the hospital ie telephone or video appointments.
- Community care: This part includes a wide set of professions including GP surgeries, NHS 24, Community nurses and community palliative care nurses,

psychiatrist, psychologist or psychotherapist, as well as physiotherapists, dietitians and occupational therapists. The mode of contact was split into practice visits, home visits from care professionals and telephone consultations.

- Charities: This component was deliberately kept in a free-text format due to the huge variety of charities which might be involved in end of life care. Items included the name of the charity, the reason the charity became involved and the treatment/help they offered, as well as the number of visits.

- Travel: The travel element included miles travelled by car and the amount which was spent on parking as well as the money paid for public or taxi transport in order to attend health care services.

Additionally, a section for out-of-pocket expenditure (OOP) was included. In a publicly funded, universal health care service such as the NHS, it might not be an integral part of patients health care expenditure, nevertheless it enabled capturing possible additional costs such as home adaptations, and cleaning services.

### 4.4.4. Domains used and Cost references

Throughout ENeRgy a variety of sources were used for costing all the resources used. They are listed in table 4.1, including the applied assumptions. Assumptions were necessary if the cost item was absent or non-identical to the one listed in the PSSRU and/or NHS reference costs.

Table 4.1. Resources used in ENeRgy, cost category, reference & assumptions

| Care/Resource used | Costs (£) | Category | Reference | Assumptions |
|---|---|---|---|---|
| Hospital Inpatient | 3720 | Hospital & Hofgspice | NHS Ref.Cost 2017/18 | Elective inpatient stay |
| Hospital Unscheduled | 626 | Hospital & Hospice | NHS Ref.Cost 2017/18 | Non-elective inpatient stay (short stay) |
| Hospice Inpatient | 404 | Hospital & Hospice | NHS Ref.Cost 2017/18 | Inpt., specialist pall. care, avg. cost/bed day |
| OOH GP Home Visit | 108.08 | OOH service | PSSRU 2012 | |
| OOH GP Phone | 27.82 | OOH service | PSSRU 2012 | |
| OP Hosp. Doc./Surg./Onco./Pall. Visits | 108 | Outpatient service | PSSRU 2017/18 | Medical consultant |
| OP Hosp. Doc./Surg./Onco./Pall. Phone | 13.2 | Outpatient service | PSSRU 2017/18 | Assume: Physician (avg. cost/e-consult.) |
| OP Clinical Nurse Specialist Visit | 87 | Outpatient service | PSSRU 2012 | Cost/hour of pat. related work (Grade 7) |
| OP Clinical Nurse Specialist Phone | 1.8 | Outpatient service | PSSRU 2017/18 | Assume: Nurse (avg. cost/e- consultation) |
| OP Physio Visit | 55 | Outpatient service | PSSRU 2012 | Cost/hour of pat. related work (Grade 7) |
| OP Dietitian Visit | 55 | Outpatient service | PSSRU 2012 | Cost/hour of pat. related work (Grade 7) |
| Comm GP Visits | 243 | Community | PSSRU 2017/18 | Cost/hour of patient related work |
| Comm Palliative Nurse Visit | 42 | Community | PSSRU 2017/18 | Cost/hour of pat. related work (Grade 7) |
| Comm District Nurse Home Visit | 41.73 | Community | PSSRU 2012 | |
| Comm Psychiatrist Visit | 341.36 | Community | PSSRU 2012 | |
| Comm Psychologist Visit | 53 | Community | PSSRU 2017/18 | Cost/hour of pat. related work (Grade 7) |
| Comm Physiotherapist Visit | 54 | Community | PSSRU 2017/18 | Comm. services (avg. cost per session/1-2-1) |
| Comm Dietitian Visit | 86 | Community | PSSRU 2017/18 | Comm. services (avg. cost per session/1-2-1) |
| Comm Occupational Therapy Visit | 78 | Community | PSSRU 2017/18 | Comm. services (avg. cost per session/1-2-1) |
| Comm Palliative Nurse Home Visit | 64.32 | Community | PSSRU 2012 | |
| MotorMiles | 0.2 | Travel | | Cost per mile |
| ParkCosts | | Travel | | As provided by patient |
| TransportCosts | | Travel | | As provided by patient |

One of the aims to include health economics in the feasibility trial was to figure which items need to be included in a questionnaire for a larger scale trial. The number of captured cost items is rather short compared to the variety of items the questionnaire provided. There are several potential explanatory factors.

- Patients were particularly well embedded in the ENeRgy trial, therefore no additional services/calls with trial team were necessary.
- It was a feasibility trial with a small sample size N=45. It is likely that a bigger patient cohort would have recorded a broader variety of resource use.

- The trial period was short (9 weeks) and in the final phase of the patient's life. Some of the items such as potential home adaptations are likely to have taken place prior to trial enrolment.

The above arguments may cast doubt on the original idea which was to omit the non-used items in the questionnaire, in any follow up trial. This perception was shared with the research nurse who was particularly clear on the fact that the trial set-up made patients feel "safe" to ask for help and ask any question; therefore being a participant within the trial reduced the need for additional care, whilst increasing not only patient satisfaction, but also contentment for informal carers and other family members. Moreover, patients were reported as asking for an extension to stay within the trial after the trial end-point.

Items which were used are from each domain in the questionnaire, whereas the informal costs and charity section were not "costed" but collected with the aim to see whether these domains may be useful in any trial roll-out.

After the first few weeks of enrolment some queries relating to questions which were challenging for patients to answer were received. All questions with regards to informal care were considered rather tricky, mainly due to an inability to distinguish between care-related and non-care related chores, and whether time off work was taken solely for care reasons. A further factor raised was that relatives might conceal some of the tasks and time taken off from the patients to make them feel less guilty. These points should be taken into account when rolling out the study and might be helpful to be included in the interviews with carers.

### 4.4.5. ENeRgy - Methods, Result, Discussion

The following section will present the methods, results and discussion section from the ENeRgy paper. The Value of Information Analysis (VOI) which was shifted to the supplementary material of the original paper is integrated in the thesis chapter. For the paper see Appendix 6.D.2 part four.

#### Methods

Health Economic endpoints examined the potential impact on patient-reported health utility, healthcare related resource use and costs. Health utility was assessed by the EQ-5D-5L and EQ-VAS patient completed questionnaires, healthcare utilisation and out of pocket expenses (Herdman et al., 2011; Pickard et al., 2007).
Questionnaires were designed to measure health-related utility healthcare related resource use and costs, administered at baseline and follow-up assessment time-points. Patient health-related quality of life was captured using a patient reported outcome measure; the EQ-5D-5L and EQ-VAS questionnaires. Utility values were assigned to responses using the standard UK value set (Bansback et al., 2012).
Healthcare utilisation and costs were collected using a bespoke patient completed questionnaire, adapted from the UK Cancer Costs Questionnaire version 2 (Hall, 2022).

Unit costs were assigned to resource use items using standard national costing sources such as PSSRU and NHS reference costs, or through consultation with relevant service business managers (NHS-Digital, 2021a; PSSRU, 2021b).
Costs were summarised from the perspectives of the NHS, the charitable and 3rd sector, and the patient and their carers. Cost-effectiveness was calculated as the Incremental Cost-effectiveness Ratio (ICER), expressed as cost per QALY gained.

A within trial cost effectiveness analysis was performed in accordance with the methodological specification of the NICE Guide to the Methods for Health Technology Assessment (NICE, 2020).

Uncertainty was evaluated using probabilistic sensitivity analysis (PSA) and value of information (VoI) analysis, implemented using the bootstrap method (1000 replications). For the PSA as well as for the VoI Analysis the SAVI Tool from the University of Sheffield was used (Strong et al., 2014).

## Health Economic Results

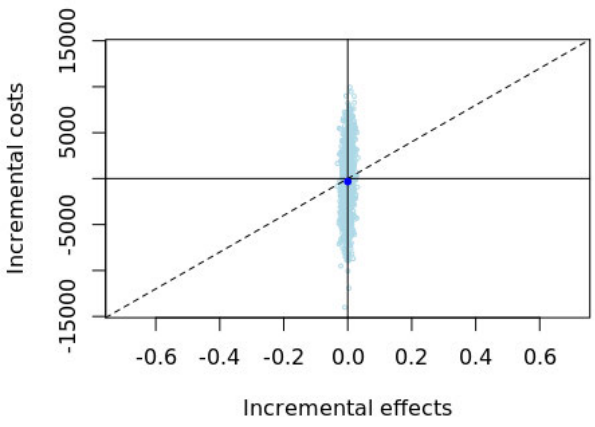
For the health economic analysis, table 4.2 details the costs, showing the cumulative mean total cost per patient at the study endpoint in the control and experimental group. Main drivers of costs were hospital inpatient stays and unscheduled hospice stays followed by community care, outpatient appointments, out of hours (OOH) services and travel costs.

Table 4.2. Mean cumulative costs per patient at study end point split by NHS-services, community care and travel

| | Hospital | Hospice | Outpatient | Community | OOH | Travel |
|---|---|---|---|---|---|---|
| Mean costs Intervention (£) | 20,380.1 | 931.0 | 77.9 | 399.1 | 49.1 | 12.3 |
| Mean costs Control (£) | 19,218.8 | 918.2 | 66.6 | 512.9 | 42.0 | 21.4 |

After adjusting for baseline EQ5D, which was similar in both arms, the mean QALYs were 0.116 [CI 0.103 - 0.129] in the control group and 0.118 [CI 0.103 - 0.132] in the experimental group. The total costs per patient across all time points in the control and experimental group were £22,239 [CI 18,155 - 26,862] and £22,508 [CI 16,623 – 27,856] respectively leading to a base case Incremental Cost Effectiveness Ratio (ICER) of £149,965.

Figure 4.1. Cost-effectiveness-plane




To explore uncertainty in the cost-effectiveness estimates, a non-parametric bootstrap with 1000 iterations was performed with the resource use and EQ5D data. The cost-effectiveness pairs are shown in the cost effectiveness plane in figure 4.1 (Briggs et al., 2006). The mean incremental cost of the experimental arm versus control is £-319.51 [CI -7593.53- 6581.91] suggesting the experimental arm to be less costly. The mean incremental benefit of the experimental arm versus control is 0.00018 QALYs [CI -0.021, 0.023] albeit not reaching statistical significance. Probabilities of the intervention being cost saving and more beneficial compared to the control group are 0.544 and 0.517 respectively.

## Discussion

The Health Economic Analysis undertaken suggested that the rehabilitation intervention was cost-saving compared to the control group. We focussed on the costs to the NHS and community care, with some indication of costs to the patients such as travel costs.

One potential reason for the cost-saving was that the care provided as part of the intervention replaced or even prevented community healthcare needs. It may also have been as a result of patients in the trial having additional attention to their wider symptom control needs (e.g. pain management) or indirect psychological support derived from the trial team.

The Health Economic Analysis is an important part of this area of research as, even if a rehabilitation programme/intervention proves to be efficacious in larger trials, if the costs associated with this were excessive, this may prohibit widespread integration into health care.
Conversely, if the rehabilitation programme/intervention was cost-saving this would support its widespread integration. Larger trials are needed to assess this further.

The trial was simply a feasibility trial and as such had several limitations, including the sample size which was under-powered for health economic analysis, particularly for estimation of costs, and this will be an important component of further research. It was also difficult to standardise background care to ensure that those in both arms received identical care with the exception of the rehabilitation intervention. This latter point is key and we cannot rule out that improvements in emotional functioning seen in the intervention arm were as a result of contact with trial staff rather than the intervention per se.

Such aspects are difficult to disentangle yet represent key considerations for future trial design.

## Value of Information Analysis (VOI)

*Brief digression*:Definition and scientific background of Value of Information Analysis? What is the rationale behind VOI Analysis and what are the benefits of including it, especially within feasibility trials?

Hall, McCabe, Stein, et al. (2012) see VOI Analysis as a framework assisting prioritisation of future research on cost-effectiveness. Wilson (2015) describes VOI as *"a quantitative method to estimate the return on investment in proposed research projects"*.

VOIs use the fact that resources can not be double spent - as a starting point. Once resources ie time, money etc are spent on an intervention they are used up and cannot be used on any alternative treatment or intervention. Therefore investing in a new intervention needs to be worthwhile, otherwise there is a risk of losing health (measured in QALYs) or resources (measured in monetary units) which could have been used if a more cost-effective option had been chosen.
Improving the information available, for example through additional research, is valuable due to a reduction of the risk of choosing a non cost-effective option (Claxton et al., 2002; Hall, McCabe, Brown, et al., 2010).

Within the umbrella of Value of Information Analysis there are several possible outcomes, of which two were used in the ENeRgy trial. The first outcome was the expected value of perfect information (EVPI) which is a maximum overall value. Secondly, the expected value of perfect parameter information (EVPPI) was in-

cluded.

The EVPI is best described as the opportunity cost of making a non cost-effective, thus wasteful decision when opting for an intervention. *The magnitude of this value is related to both the estimated cost-effectiveness and the current level of uncertainty about the cost-effectiveness estimate* (Hall, McCabe, Stein, et al., 2012). The EVPPI is offering similar information limited to a single parameter or a group of parameters.

The University of Sheffield's research group running the SAVI tool, which is widely based on Strong et al. (2014) describe VOI-Analysis as follows: *One can visualise this idea by imagining that instead of seeing the cloud of dots on the cost-effectiveness plane (representing current uncertainty in costs and benefits) and having to choose, the decision maker now knows exactly which dot is the true value.* All uncertainty of the decision is removed and the best strategy can be chosen with certainty.
When comparing a new intervention to standard care this would mean any dot above and to the left of the threshold will point towards keeping the current care whereas a dot below and to the right would indicate that the new intervention should be adapted. With uncertainty the decision will be based on *the expected costs and benefits (essentially on whether the centre of gravity of the cloud is above or below the threshold line).*

To sum up the aim is to reach reduce uncertainty surrounding the model parameters to enable the decision maker to choose from a variety of strategies with improved knowledge (due to the reduced uncertainty) of the best option.
VOI Analysis is a valuable decision tool in the question whether further research (especially when planning to roll out feasibility trials on a bigger scale), including clinical trials or observational research, is beneficial and it can give some information

about useful research focuses (Hall, McCabe, Stein, et al., 2012).

## VOI Analysis in ENeRgy - Overall EVPI

The overall EVPI per person affected by the decision was estimated at £1297.2 per person. This is equivalent to 0.06486 QALY per person in decision uncertainty when valuing uncertainty on the QALY scale.

Assuming an annual number of people affected by the decision of 1000, the overall EVPI per year is £1.3 million for the UK see table 4.3.

Table 4.3. Expected Value of Perfect Information (EVPI) per person

| | Overall EVPI (£) | Overall EVPI (QALY) |
|---|---|---|
| Per Person Affected by the Decision | 1297 | 6.486e-02 |
| Per Year in UK "1000 people affected/year" | 1297000 | 6.486e+01 |
| Over 5 Years | 6486000 | 3.243e+02 |
| Over 10 Years | 12970000 | 6.486e+02 |
| Over Specified Decision Horizon (20 years) | 25940000 | 1.297e+03 |

When thinking about the overall expected value of removing decision uncertainty, it is necessary to consider how long the current comparison will remain relevant. Assuming a 20 year pertinent time-horizon at a 3.5% discount rate for costs and benefits, the maximum value of a perfect research study to the UK population is £25.9 million. Research or data collection exercises costing more than this amount would not be considered cost-effective use of resources.

The EVPI estimates (in table 4.3) quantify the expected value to decision makers within the jurisdiction of removing all current decision uncertainty at a threshold of £20,000 per QALY.

## Single Parameter EVPPI

Partial EVPI enables identification of those parameters that contribute particularly highly to decision uncertainty. For each parameter, the expected value of removing current uncertainty is displayed in the table below.

Table 4.4. Expected value of perfect parameter information (EVPPI) for single parameters

| | Per Person EVPPI (£) | Standard Error | Index to All EVPI = 1.00 | EVPPI for UK/year (£) | EVPPI for UK/20 years (£) |
|---|---|---|---|---|---|
| cost_int | 984.36 | 40.52 | 0.76 | 984400 | 19690000 |
| cost_con | 755.02 | 50.70 | 0.58 | 755000 | 15100000 |
| QALY_int | 6.24 | 26.50 | 0.00 | 6238 | 124800 |
| QALY_con | 75.90 | 43.55 | 0.06 | 75900 | 1518000 |

## EVPPI for Cost and QALY difference

Although EVPPI information about individual parameters is useful, often it is more informative if EVPPI can be computed for groups of associated parameters e.g. all parameters associated with efficacy data. This will enable a maximum value to be put on further research to jointly inform this set of parameters.

Table 4.5. Expected value of perfect parameter information (EVPPI) for grouped parameters

| | Per Person EVPPI | Standard Error | Indexed to Overall EVPI = 1.00 | EVPPI for UK/20 years (£) |
|---|---|---|---|---|
| Difference in Costs | 1295.43 | 4.34 | 0.99 | 25910000 |
| Difference in QALYs | 60.15 | 42.81 | 0.05 | 1203000 |

Looking at the parameters it can be seen that the Expected value of perfect parameter information is very high for the Cost difference and comparably low for the quality of life component.

## 4.5. Learning outcomes and observations

The two trials serving as case studies are vastly different; starting from the intensity of involvement, collection of data, costing, write up, depth of analysis and other reasons. Both provided a great opportunity for learning.

### Learning Outcomes EPAT

The study's health economic potential was limited due to the fact that the health economic component was started and integrated at a late stage. If health economics had been included at the setup the collection of resource use could have covered care components over and above medication use and inpatient time.

Potential variables of interest include, clinical treatments besides pain related interventions, in depth care activity and some information on comorbidities such as the Charlson Comorbidity Index (CCI) (Sundararajan et al., 2004).
The focus on inpatient cost and the fact that there was no information about the patients post-discharge was discussed as a major limitation. We are unsure whether the slightly earlier discharge led to more hospitalisations further down the line and if there were differences due to variations in community services.
It could be argued that those patients with good community services in place were discharged earlier as they had the option for support and it might be argued that they were less likely to attend the hospital later on. Nevertheless the main variables of interest were collected and significant differences were shown.

This study sparked some discussion between the health economists within the team as to whether it is feasible to conduct a health economic analysis coming into a

trial at that late stage, without any prior involvement in the study's setup and questionnaire development, and therefore without prior knowledge of the variables collected and the "condition" of the database.

The data were held within the palliative care unit, which made data access relatively straightforward. Nevertheless, the handling of the data provided ample opportunity for shared learning.
After the first meeting with some members of the original trial team it was suggested that data would be shared via mail. Considering the nature of the data, it was decided to use of the University run Dropbox-like file hosting service 'DataSync' instead to provide some support in the setup and handling.
Unblinded data were shared - nevertheless the overall data and its split into different files was quite convoluted, so it was not actually 'unblinded' until the randomisation variable was clarified. Another complicating factor was that there was no data dictionary (available) as everyone involved in the trial so far had been part of the initial study team - therefore it had not been deemed necessary.

The work within the study was a rather lengthy costing exercise for the medication section, with a manual lookup of drug costs in the British National Formulary. Costs for specified pain interventions and for inpatient stays were taken from NHS reference costs unless otherwise stated in the assumption section.

No 'time cost' was assumed for performing the more strategic approach to assessing the pain, as it can be assumed, that pain is discussed anyway- only the way of assessing pain is more directed when using the EPAT tool. The use of EPAT might even turn out to be time saving as it streamlines the conversation about pain and is helps patients to find the 'right' description.

The overall verdict; Is it worth doing a health economic analysis coming in at that stage? Yes, but be prepared for a few challenges!

Coming in at a late stage, and the fact that the study was run outside a trials unit, thereby having a different infrastructure, added some challenges. A major issue was the fact that the original trial did not include health economics. This led to the study being under-powered for reaching significant results. Nevertheless, as data were already collected and readily available and some health economic analysis was possible, it was decided to exploit the opportunity.

## Learning Outcomes ENeRgy

In the ENeRgy trial, health economic involvement started at the setup phase and was integral to the whole process. Being part of the discussions for the setup was beneficial as it enabled a detailed overview of the proposed trial outcomes, the exact strategy, giving and receiving feedback on the questionnaire development and the proposed analysis, as well as coordination of the variables collected with the statistics team. This can be beneficial in order to keep the patient burden low by avoiding to collect similar variables twice.

At the start of the data collection one of the questions on the follow-up questionnaire was deemed unclear, but due to the close cooperation it was immediately brought to attention and could be clarified. The data analysis was straightforward due to the high engagement of the research nurse, which left the data with a very low number of missing variables. The write up was done from clinical, statistical, qualitative and health economics perspectives separately before being brought together into one paper.

The drafts were collaboratively reworked until it was ready for publication. De-

spite the health economics section in the final publication being concise, all the performed analyses were worthwhile as they can inform the development of a phase 3 study and are part of the PhD, and as such play an important role in this thesis.

## Overall Learning

The sources of care activity data from the included trials were based on trial specific data collection. The variables needed for the health economic section were included in the Case Report Forms (CRFs). Whilst involvement in the EPAT trial started later, ENeRgy's health economics questionnaire was developed in advance, discussed by the overall trial team before being integrated in the CRF. Variables on resource use collection include hospital-based care, primary and community care along with data on informal caregivers' time, travel costs and the involvement of charities (Hall, Norris, et al., 2018; Hall, Skipworth, et al., 2021).

Setting up data collection for a specific trial, eventually creating a separate questionnaire, enables a very detailed collection of most resources used. Nevertheless these data often face restrictions due to small sample size and being very specific to a particular setting, limiting potential generalisability.

Creating a trial specific questionnaire enables researchers to capture resource use and costs from all aspects of life. In the ENeRgy trial, the cancer-UK questionnaire was adapted and extended specifically for the trial in order to fit with a broader range of services used across several disease types, and to be suitable for a palliative setting. It does not include the costs of informal care but rather a collection, in order to understand better what would need to be collected in a roll out.

Primary data collection is well suited for comparing predefined groups especially if

it is reasonable to assume that an intervention is "just influencing a certain aspect of resource use", whilst all other elements remain constant; - but is that true? It is almost certainly more complex than this.

Collecting data within a trial needs to be thoroughly planned beforehand (as can be seen within the projects included) - otherwise it will be very restricted in the types of analysis which are possible.

Research during the last phase of life can be seen as a burden by patients, relatives and care professionals, therefore it is essential to keep questionnaires and interviews as concise as possible. The challenge is not to lose the opportunity to collect in depth data. Despite the end of life being an emotional and stressful phase, patients and relatives are frequently reported to be a particularly willing cohort for involvement in research as they often want to give something "back", if they are satisfied with the care they receive. Further they are motivated to help improve the circumstances for subsequent patients, if satisfaction was low. Nevertheless questionnaires, as well as interviews, need to be centred around variables of interest as time limits can be a major factor. A practical example within this thesis, is the feasibility trial ENeRgy, which included more components than patients filled in. Therefore, it is inherent on the researchers and members of the Patient and Public Involvement groups (PPIs) to decide which questionnaire items are most important to include in a phase 3 study.

Despite it being essential to include informal care, it will remain challenging to define care "what was done just for the patient vs. what would have been done within the household anyway". This makes it particularly difficult to define the time spent on care and put a cost on it. The only item which seems straightforward to

capture is any time relatives need to take off work; but how to cost all the remaining "care-time" is challenging.

Overall huge improvements can be observed over the last decade with regards to trial set up and planning. Health economic involvement is now frequently integrated from the beginning of the trials and often an integral part of feasibility trials. This enables us to capture all variables needed instead of relying too heavily on assumptions.

# Chapter 5

## Discussion, Potential Solutions and Conclusion

## 5.1. Discussion

On reflection of the thesis aims and the papers presented within this work, it becomes apparent that the field of health economics, especially within in the context of end of life care, is still very much under development. Clear methodological guidelines with regards to resource use data collection and costing approaches are needed. The subsequent section includes a discussion of the current landscape, reflections on the predominant challenges, and highlights some of the key insights gained.

**Definition of end of life care and time-frame of the "end of life"**

Although the broad definitions for "end of life" as defined by the European Association for Palliative Care (EAPC) and the General Medical Council (GMC) are relatively similar, they are quite vague in terms of defining a clear time frame. Whilst, the definition provided by EAPC reports an approximate timeline of one to two years during which the life-limiting nature of an illness becomes obvious. The GMC defines the "end of life" as when there is a high likelihood for an individual to die within the next 12 months (GMC, 2019; Radbruch and Payne, 2009).

The administrative data studies included, chose a time-frame of one year prior to death; depending on the end of life definition applied, this could be interpreted as a limitation. Aside from the difference between EAPCs and GMCs definitions, it is not possible to define a clear point from which an individual patient enters their "end of life" stage. Depending on the type of disease as in Diernberger, Luta, Bowden, Fallon, et al. (2021) or the type of cancer as in Diernberger, Luta, Bowden, Droney, et al. (2022) a patient's "end of life state" could have been ongoing farlonger than a year, as is likely with a primary cause of death such as dementia, or

be much shorter especially when looking at "aggressive" cancer types such as many haematological cancers with a likely time-frame from diagnosis to death of less than a year.

The uncertainty surrounding the timing of the end of life stage is reflected in the variability observed in study periods across the studies included in the updated systematic literature review (Chapter 2) and studies presented in this thesis.
Whilst some studies have used a (i) relatively short time period such as the last three months or final 90 days as in Georghiou and Bardsley (2014), Hollingworth et al. (2016), and Yi et al. (2020), (ii) many have applied a much longer time frame (e.g. a year as in Diernberger, Luta, Bowden, Droney, et al. (2022), Diernberger, Luta, Bowden, Fallon, et al. (2021), Jayatunga et al. (2020), Luta, Diernberger, Bowden, Droney, Hall, et al. (2022), Luta, Diernberger, Bowden, Droney, Howdon, et al. (2020), and McBride et al. (2011)) or (iii) used a specific event in the patient's history as a starting point, such as described in Guest et al. (2006) and Round et al. (2015), who used the initiation of strong opioids as the starting point of their study period. An alternative definition used, as demonstrated by Johnston et al. (2012), is the date at which a life-limiting illness is diagnosed.

In the studies by Diernberger, Luta, Bowden, Droney, et al. (2022), Diernberger, Luta, Bowden, Fallon, et al. (2021), Luta, Diernberger, Bowden, Droney, Hall, et al. (2022), and Luta, Diernberger, Bowden, Droney, Howdon, et al. (2020) a prognosis of one year prior to death was chosen due to availability of data which were part of a wider research programme.
Most studies did not provide a justification of their study period such as Bardsley et al. (2010), Coyle et al. (1999), Georghiou and Bardsley (2014), Hatziandreu et al. (2008), Hollingworth et al. (2016), and McBride et al. (2011), or vaguely mention

that the last phase of life amounts to a considerable share of the country's health care budget or GPD as in Jayatunga et al. (2020) and Yi et al. (2020).

This inconsistency in the length of study period and the lack of provision of the underlying rationale make it difficult to compare or synthesise findings across different studies which aim to answer the same question.

**Data collection and deriving costs**

Further inconsistencies in methodology which hinder comparability were (i) the use of different data sources ie the *source of activity data* including applied data linkage and (ii) differences in the costing methods applied ie the *source of unit costs*.

Most of the studies identified in the literature review used similar *data sources*; Hatziandreu et al. (2008) and Hollingworth et al. (2016) utilised hospital episode statistics (HES) to capture hospital based care activity. Similarly the data inputed into the models by McBride et al. (2011) and Round et al. (2015) were partially informed by HES data.
Nevertheless the above studies used HES data in substantially different ways. Whilst McBride et al. (2011) and Round et al. (2015) solely informed some of the model parameters included, Hatziandreu et al. (2008) linked HES data to data from the Office of National Statistics (ONS), the Minimum Dataset (MDS) and data from the National Council of Palliative Care (NCPC). Hollingworth et al. (2016) linked HES data to the Clinical Practice Research Datalink (CRPD).

The administrative data studies included in this thesis were Scotland-based, hence data were linked using the CHI number and included data on hospital based activity (SMR00, SMR01 the second study additionally included SMR06) and data on

death statistics informed by the National Records of Scotland (Diernberger, Luta, Bowden, Droney, et al., 2022; Diernberger, Luta, Bowden, Fallon, et al., 2021). One of the major limitations of the Scottish administrative databases was the inability to link them to data from other care settings.

Despite primary care data being theoretically available for research purposes in Scotland, it cannot yet be easily linked to secondary care data. To gain an overall understanding of resource use at the end of life, secondary care data needs to be linked to primary, social and community care data and in a best case scenario include data on informal care.

Most health economic studies aim to incorporate at least a health system perspective (in this case NHS Scotland), however limitations in the ability to link Scottish administrative data from different settings meant that the perspective chosen in the administrative data studies ended up being rather narrow (Diernberger, Luta, Bowden, Droney, et al., 2022; Diernberger, Luta, Bowden, Fallon, et al., 2021).

By comparison, the studies based on an English population by Luta, Diernberger, Bowden, Droney, Hall, et al. (2022) and Luta, Diernberger, Bowden, Droney, Howdon, et al. (2020) do include GP-based care activity, hence were more closely aligned to a broader NHS perspective.

The sources of care activity data in the included trials were based on trial specific data collection. The variables needed for health economic analysis were included in the Case Report Forms (CRFs).

Whilst involvement in the EPAT trial started late, ENeRgy's health economics questionnaire was developed in advance and discussed by the interdisciplinary trial team prior to the integration into the trial's CRFs. Variables on resource use collection included hospital-based, primary and community care alongside data collected

on informal caregivers' time, motor miles and the involvement of charities (Hall, Norris, et al., 2018; Hall, Skipworth, et al., 2021).

The second major factor potentially limiting studies' comparability is the source of *unit costs*.

The costing approach used in the administrative data studies relied heavily on the Scottish health service costs, known as the Scottish Cost Book, detailing cost information for NHS Scotland. Financial and statistical data are provided by the 14 Scottish health boards (ISD, 2019). Both, the Scottish Cost Book as well as English reference costs as used in Dzingina et al. (2017), Georghiou and Bardsley (2014), Hollingworth et al. (2016), Jayatunga et al. (2020), Johnston et al. (2012), and Round et al. (2015) detail average unit costs for providing defined services, first for Scotland later for England (NHS-Digital, 2021a).

There is some uncertainty about how much variation is due to the costing method applied. A paper by Geue, Lewsey, et al. (2012) scrutinised hospital-based costs by applying different costing methods to the same dataset. HRG (Healthcare Resource Group) based costing (for England and Scotland tariffs separately) was compared to a "per diem costing" approach and "per episode costing". Results highlighted significant differences in costs based on the method chosen. The authors recommended HRG based costing methods as used in the included studies; mainly as they take the nature of a disease and the connected expected LOS (length of stay) into account.

Costing approaches used within the included clinical trials, as well as the trials identified in the literature review, commonly included a mix of NHS reference costs and PSSRU costs (Brick et al., 2017; Dzingina et al., 2017; Georghiou and Bardsley, 2014; Hall, Skipworth, et al., 2021; Hollingworth et al., 2016; Round et al.,

2015). Depending on the study, additional costs such as drug costs were of particular interest ie in the EPAT study and two of the studies identified in the literature review namely Guest et al. (2006) and Hollingworth et al. (2016). Unit costs for drugs were taken from "NHS prescribing data" as in Hollingworth et al. (2016) or "MIMS" (Monthly Index of Medical Specialties) and the "Drug Tariff" as in Guest et al. (2006). The drug tariff includes more information than the prescription data for medication, namely reimbursement for NHS services provided by the pharmacy, drug and appliance prices as well as fees and allowances paid (NHS-Payment-System, 2021). The drug prices in EPAT were informed using "BNF" (British National Formulary) costs, which are based on "Drug Tariff" prices.

**Additional considerations and findings**

The second administrative data study included all patients with an entry in the Cancer Registry (SMR06) - not solely those with cancer as a listed cause of death. Differences in resource use of patients having an entry in the cancer registry and those with an entry in the registry and cancer as a listed cause of death (75%) were highlighted. Patients who had a cancer diagnosis and died from cancer tended to be younger and used more health care resources compared to those with another cause of death.

Further, the assumption that all cancer patients are resource intense in their last year of life was shown not to hold for specific cancer types. Whilst this assumption is certainly true for resource use intense cancers such as haematological cancers, hardly any difference in costs was observed between patients who did not die from cancer and those who died from lung cancer. Nevertheless it is not clear if this result is based on the overall resource intensity of the cancer treatment or the timing of the

treatment. It is possible that most of the costs connected to treating lung cancers occur prior to patients' last year of life and were therefore missed due to the study design.

Clear interactions were demonstrated between age and tumour type, with different tumour types requiring different levels of care intensity. Despite the results being once again restricted by the study design ie only including patients of 60 years and older, the mean age at death varied between cancer types, with the cohort of brain cancer decedents being on average five years younger at their date of death than breast cancer decedents.

Another point adding to the complexity is the observation that age and comorbidity burden impact costs in opposing ways. Whilst costs decrease with older age, they increase with added comorbidity burden. Contrary to the popular believe that higher age comes with a higher level of comorbidity burden, our cancer study showed a significant negative correlation, which might partially explain the big drop in costs for the older population. Nevertheless, it remains unclear how much of these effects are captured in the study, as it is possible that most of the comorbidity burden is dealt with prior to entering the final year of life and/or outside hospital-based care. Further research, preferably using administrative data (as a high number of comorbidities are a frequent exclusion criteria within clinical trials) is needed to unpick this complex relationship.

The administrative data studies solely include decedents, not showing patient pathways for curative outcomes. Looking at decedents only can theoretically lead to an increase as well as a decrease in resources used as outlined in the subsequent sections:

There is a need for estimates that align with the policy objective that the estimates

are trying to inform. For example the budget impact of a changing demography such as a higher average age at death, requires estimates that adjust for changing causes of death and other factors.

Whilst the red herring hypotheses points towards health care resources being highest in close proximity to death and not necessarily being linked to age, other hypotheses exist ie the hypothesis of morbidity compression. This hypothesis describes the development that the length of lifetime spent in states of chronic disease and disability is not only shifting back to a older age but is generally decreasing (Fries, 1996; Zweifel, 2022).

In contrast to the morbidity compression hypothesis, the morbidity expansion hypothesis states that despite the lengthening of life, the additional life years are spent in ill health - therefore leading to an increase in overall health care costs (Olshansky et al., 1991).

Further, there is the idea that "well planned" end of life care such as advanced care planning (ACP) is leading to a more realistic outlook for patients and relatives, to cost savings and a reduction in hospitalisations (Jimenez et al., 2019; Klingler et al., 2016; NICE, 2022a).

In order to understand which hypotheses are applicable to an UK setting, it is imperative to look at data including primary care and community care, as it can be assumed that good care planning is leading to a shift in the type of health care resources used and not necessarily leading to a reduction of overall use.

If the general policy interest is not focused on understanding the underlying mechanisms which drive resource use, but instead is leaning more towards analysing the cost effectiveness of new end of life care interventions and changes to current practice (Cost Effectiveness or Cost Utility Analysis based) there might be no need

for adjustments for age and or comorbidity.

*Note:* Cost- Effectiveness Analysis and Cost-Utility Analysis short CEA and CUA compare two or more interventions, or a new intervention to the status quo, by estimating how much money is needed to gain a unit of a health outcome. In CEA the unit of health outcome can be for example a life year gained or a death prevented, whereas in CUA the outcome is reported in QALYs.

Another possible approach to strengthen the knowledge base includes being able to identify all the individual resource inputs of interest and have a more micro-costing approach such as a detailed estimates of staff time, theatre time, medicines etc and not only bundled costs.

An additional consideration and one of the big drawbacks of working with administrative data is the lengthy process prior to gaining data access and the governance around and the reliability of safe havens. Apart from this leading to study results which are dated at the time of publication hence do not reflect newer developments such as big political changes (eg BREXIT) or potential needs, (eg a re-prioritisation due to unforeseen circumstances such as a pandemic (COVID19)) there are still other challenges to be overcome, most of them regarding workability.

**Strengths and limitations of this thesis**

This thesis includes an update of a systematic review, covering the existing literature on resource use in end-of-life care in the UK up to October 2021, and includes end of life care resource use and costing studies, involving either an analysis of administrative data or cost analyses alongside clinical trials.

To ensure the inclusion not only of a substantial breadth of data but added depth,

clinical trials were included in this work. Despite the second trial being a feasibility trial, hence being limited by a small sample size, it provides insights into resources used outside secondary care. EPAT further adds depth by demonstrating some insight into medication costs.

A considerable limitation in all studies is the sparse information on the influence of informal care and charities, which is assumed to be a substantial part of the end of life care landscape in the UK. Though comprehensive data on charities might be difficult to capture due to them frequently being focused on specific illnesses and expected regional variations, a stronger focus on the services provided by the charities and the connected costs is recommended. Within projects included in this work, only ENeRgy incorporated some elements of data collection on informal care and gathered data on the involvement of charities.

Despite the administrative data studies' limitation of solely including secondary care data, they capture a considerable share of the overall healthcare costs and provide substantial knowledge of the Scottish end of life care costs. By using national data, it is possible to include the whole population, providing greater certainty compared to trial data that the study outcomes are nationally representative. Nevertheless it needs to be acknowledged that that these papers scope is too narrow (limited to secondary care data) to inform decision making.
Further, there was a strong reliance on average values which means that potentially useful information was not fully exploited.

The studies' choice of methods were based on literature and were in line with recommendations by Glick et al. (2014), Hazra et al. (2018), and Moran et al. (2007). The studies included in the thesis, as well as the English studies which were con-

ducted under the same research project, are amongst the first to breakdown the patient cohort by Cause of Death (Diernberger, Luta, Bowden, Droney, et al., 2022; Diernberger, Luta, Bowden, Fallon, et al., 2021; Luta, Diernberger, Bowden, Droney, Hall, et al., 2022; Luta, Diernberger, Bowden, Droney, Howdon, et al., 2020).
In the context of the existing literature in this area, they are likely to be the best estimates yet for end of life secondary care costs in Scotland.

## 5.2. Potential solutions and recommendations for further research.

In order to understand, a) which of the hypotheses around resource use and costs at the end of life prove true and b) to understand whether policy interventions tailored to the end of life are truly saving resources or "just shifting" the burden from the hospital sector into primary care, community care, charity funded care or informal care, we need to find a way to include a broader variety of data sources into big data studies.
A big substitution effect is assumed between hospital-based care and primary care, for which data should theoretically be available. The "Scottish Primary Care Information Resources (SPIRE)" are collecting data at GP practices and are reporting on certain points of interest available for the individual practice. Despite there being plans to provide data also for research, they are not yet fit for linkage.

Next to including more "types" of resource use, studies definitely become more powerful when adding quality of life components adequate for capturing end of life care needs.
As administrative data are not collecting patient reported outcome measures (PROMs)

or other quality indicators, it might be a promising approach to combine data collected within trials with administrative data. Informing resource use/cost side by using administrative data and just adding the qualitative components (and the missing resource use parts such as charity involvement and informal care) through questionnaire based data collection, could provide a high data density whilst keeping the patient burden low.

Despite the above theoretically being an "easy and efficient" way to gather data, there are some doubts that progress in this direction is fast, especially when keeping the barriers to access administrative data and all rules regarding data governance and safe haven involvement in mind.
This basically brings back the question asked by Bain et al. (1997) as to whether routinely collected data is fit for purpose. It can be stated that some of the restrictions highlighted nearly 25 years ago still apply. There are remaining gaps in the collected data, as routine data is primarily collected for administrative purposes and not for research. Further, despite great progress within this section (eg Scotland using CHI numbers which allows for data linkage) there are still some issues in combining different data sources mainly connected to the remaining challenges around data confidentiality and ethical considerations.

Despite all the identified shortcomings of using administrative data it is a valuable source for research and not yet fully exploited. It could for example be used to conduct natural experiment studies. Some of which were conducted relating to the COVID pandemic. Another interesting starting point could be policy changes, the effect of which could than be measured in routinely collected data.

A potential improvement to end of life research in relation to trials could include

"semi-standardised" questionnaires for trial based resource use collection. Naturally questionnaires need to be adaptable to individual trials. Nevertheless having one template to start from, could eliminate some of the variation. Further it might be a good "reminder" to collect resource use connected to charities and informal care when striving for a trial tailored to the patient perspective.

Similar to standardizing data collection, overall "costing guidelines" included next to the data collection, the recommended source of activity data and the source of unit costs might reduce some of the factors currently limiting comparability. Naturally these guidelines would need to be tailored to end of life care studies and limited to areas which rely on the same system for data collection and unit costs, such as for example guidelines limited to Scotland. Special attention would be needed to tailor guidelines to an end of life care setting.

It is worth noting, that it remains unfeasible to compare end of life care interventions to curative care ones, especially when trying to use the same "willingness-to-pay threshold" when declaring an intervention as cost-effective or not. There are too many unresolved issues connected to resource use collection and costing, methodological issues and a whole new set of challenges when dealing with quality of life.

## 5.3. Conclusion

Despite this thesis pointing out several shortcomings of palliative and end of life care research, compared with most countries presented in the Global Atlas of Palliative Care WHPCA (2020), the UK is within the leading group of countries. There seems to be a general consensus about the importance of end of life and palliative

care, but still too little is known about the unique nature of this phase in life and its connected needs.

End of life care is substantially different from curative care, with the latter being mostly limited to short spells of primary or secondary care with some outpatient care, whilst at the end of life an "all-round care package" is frequently required. Apart from the variation in locations, intensity of care and carers involved, there are several issues complicating the matter and limiting comparability between and generalisability of studies. Studies use a variety of perspectives, are run in and across different health care systems (and may even have regional variations within a single system), identify different variables for capturing resource use and use a variety of costing approaches.
Overall the multifaceted nature of care needed makes the collection of resources used and the costing process very complex. Whilst some of these points, such as differences in the underlying structure within and across health care systems, are challenging to tackle it seems possible to find solutions for others.

An important first step could be made by introducing guidelines with regards to (i) the perspective of interest (ii) a more standardised time-frame of the end of life stage applied in research, (iii) a systematic approach to data collection and (iv) recommendations regarding the source of unit costs and costing methods applied.

As all of us will inevitably die it should be in everyone's interests to find ways to improve care provided during this crucial stage of life. Streamlining research and aligning research outcomes are key to strengthening the position of palliative and end of life care.

It is important to keep in mind that in the end we are not able to change the outcome,

but we are able to influence the experience of patients and their loved ones along this challenging journey.

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# Chapter 6

## Appendices

# Appendix - Introduction

## 6.A.1. Incompatible: end-of-life care and health economics

# Incompatible: end-of-life care and health economics

Katharina Diernberger,[1] Bethany Shinkins,[2] Peter Hall,[1] Stein Kaasa,[3] Marie Fallon [4]

> When it comes to death, the statistics are stark. 100% of us will die. The question is what are we all going to do about that? How are we going to create confidence in the care that we may need?[1]

During the last year of life, major healthcare resources are spent, not only in lifetime monetary terms, but also on professional time. Reflecting on this quote, it seems counterintuitive that health economics could play a major role in tackling the main challenges in end of life care. However, the escalating cost of healthcare, combined with an ever-increasing range of therapeutic and patient management options, has brought difficult budget allocation decisions to the fore.

## WHAT IS THE VALUE OF HEALTH CARE?

The value of healthcare can be considered as what is gained relative to what is lost. In our context, there are three value dimensions:

1. Population: how well assets are distributed to different subgroups in society (equity in resource distribution).
2. Technical: how well resources are used for outcomes for all people in need in the population (improving quality and safety of services).
3. Personal: how well the outcome relates to the values of each individual (understanding what matters most to the patient).

Contrary to popular misconception, value is not the same as quality of care or how much money is spent. High-quality care to the wrong patient or at the wrong time (or in the wrong place), is still low value. Similarly, better value is not necessarily achieved by more money. Nevertheless, even to the right person at the right time, it will still have an inevitable cost

However, maximising value in healthcare resources requires understanding both what we seek to achieve and the effectiveness of the means to achieve it; this is the purpose of health economics.

People used to a universal healthcare system may struggle to see the value of healthcare, rather than perceive it as a basic right and rarely question where these resources originate.

## WHAT IS HEALTH ECONOMICS?

*'Economics is a science which studies human behaviour as a relationship between ends and scarce means which have alternative use'*.[2] Thus, economics is a science of choice. Health economics is therefore the science of choice within the healthcare context. The aim is to distribute a constrained health budget to maximise overall population health.

A key concept of economic theory is 'opportunity cost', defined as '*(t)he value of forgone benefit which could be obtained from a resource in its next best alternative use*'.[3] Fundamentally, money spent on a certain intervention/treatment/drug cannot be spent on something else—even though that may also have had a beneficial outcome. In reality, healthcare systems are so complex that the opportunity cost is typically NOT identifiable, that is, we do not know what other healthcare intervention we may have displaced.

The economic evaluation framework quantifies the pros and cons of specific health interventions and balances them against the cost (which might be to the system or the individual). With such a framework, we can therefore reduce 'waste' by identifying and exchanging treatments that may be of minimal benefit for more effective ones.

## HEALTH ECONOMICS AND PALLIATIVE CARE

The care of terminal or highly symptomatic disease is expensive, with both a financial and capacity strain on individuals and local and national health systems globally. This is exacerbated by a demographic shift in age distribution; people live longer with more health needs in later life. Medical and technological advances expand treatment options, many at great cost. For example, new anticancer treatments, like immunotherapies and targeted anticancer therapies improve progression-free survival, sometimes overall survival but significantly increase costs at end of life. Drugs recently approved by the National Institute for Health and Care Excellence (NICE) for poor prognosis cancers typically cost about an extra £50 000 for each quality of life-adjusted year (QALY) gained—a composite measure of individual quality of life and survival.

As the healthcare budget is constrained, hard choices must be made. Real patient care has numerous challenges and limits on finance and appropriate healthcare worker time. One important example is community care, which is largely dependent on the number of available informal carers. Prioritising between this type of care and palliative anticancer treatments is an inherent tension. Health Economic

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evaluations assist decision making on a larger scale, like the choice between additional palliative care beds or new drugs and more intensive care.

## PROBLEMS OF HEALTH ECONOMICS IN PALLIATIVE CARE

As health economics informs decision making, influencing the quantity, quality and sustainability of healthcare resources, it is imperative this methodology is applied to the highest possible standards. Within the UK, a standard approach to compare the cost-effectiveness of interventions has been established by decision makers like NICE. It relies on the costs to the National Health Service (NHS) and social care balanced against differences in QALYs.

For several reasons, this approach falls short when evaluating interventions at the end of life.

- First, a significant proportion of the important costs are likely to be incurred outside of the NHS, the charitable sector, the welfare state or the individual and their families and/or carers. These currently fall outside of a NICE standard economic evaluation.
- Second, it is inaccurate to measure patient benefits because the improved function is not expected. The standard methods for quantifying health outcomes are problematic in end-of-life care as the patient needs/focus are different than in those expected to improve.
- Third, the QALY is the recommended tool for capturing health outcomes across different clinical and disease areas. However, the ability of the QALY to capture aspects of health important to patients in an end-of-life context has been questioned given the aim at that juncture is neither improved survival nor function. The aims are to prevent and treat symptoms, preserve function, shared decision making and family care.

New research programmes are testing different strategies of better capturing patients' priorities at the end of life like the burden of illness measures or palliative-specific quality of life measurements such as Investigative Choice Experiments of CAPablility measures.

## WHY IS IT URGENT?

Worldwide, the financial cost to an individual with severe illness is significant. In the USA, the risk of bankruptcy increases by 250% with a cancer diagnosis.[4] Even in the UK where healthcare is free at delivery, those with a cancer diagnosis were found, on a monthly average, to be £570 poorer.[5]

In the UK, most people die in hospital, despite it being the least preferred location.[6] Many may have unnecessary clinical interventions unlikely to impact quality and/or length of life.[7] Hospital care is expensive but comprehensive palliative care at home may also be costly.

Tailored end-of-life care integrated into public healthcare reduces emergency hospital and intensive care unit admissions and length of hospital stay.[8 9] A more personalised approach therefore has great potential to avoid unnecessary resource use while simultaneously benefitting the patient.

In the UK, all these issues are being tackled by a new national strategy to redesign palliative care services. But is it a need to prioritise, for example, between expensive new drugs with limited life prolongation and little evidence of improved symptom management or a basic human right to good end of life care? In line with national ambitions for personalised care, advanced care planning is at the heart of this strategy, where patients should have realistic high-quality choices at the end of life.[1 10] The effectiveness of sustainable integrated palliative care programmes[11]—including the funding of end-of-life services—is well documented[12] and it may be best to prioritise such interventions in a public health system.

> How much a society is able and prepared to spend on those who are sick and face approaching death may differ; views will vary across (and within) continents and countries and between faith and value systems.[13]

The goal therefore should be to reduce the financial burden of care of the dying on the healthcare system without compromising the level of care or a person's quality of life. If the palliative care clinical community accepts available resources are constrained, then extensive work is necessary to better understand the value at the end of life.

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# Appendix - Systematic Review

### 6.B.1. Search strategy and outputs

Table 6.1. Search query and output from CINAHL and MEDLINE

| Query | Limiters&Expanders | Last Run Via | Results |
|---|---|---|---|
| (Palliative care OR terminal care OR terminally ill OR end of life care OR hospice OR life limiting) AND (Health expenditure OR health care costs OR costs and cost analysis OR economic assessment OR economic evaluation OR economic implications OR resource utilization OR resource consumption OR health care utilization OR financial burden OR financial stress OR financial strain) AND (UK or England OR Wales OR Northern Ireland OR Scotland) | Limiters – Published Date 20171001 – 20211031; Publication Year: 2017-2022; Age Groups: All Adult; Age Related: All Adult: 19+ years; Search modes – Boolean/Phrase | Interface – EBSCOhost Research Databases; Search Screen – Advanced search; Database – CINAHL Plus; MEDLINE | 88 |

Table 6.2. Search query and output from Psycinfo

| # | Query | Results Oct 2021 |
|---|---|---|
| 1 | (Palliative adj1 care).af. | 35,886 |
| 2 | (terminal adj1 care).af. | 6,069 |
| 3 | (terminally adj1 ill).af. | 14,038 |
| 4 | (end adj1 of adj1 life adj1 care).af. | 13,875 |
| 5 | hospice.af. | 20,075 |
| 6 | (life adj1 limiting).af. | 2,285 |
| 7 | 1 or 2 or 3 or 4 or 5 or 6 | 51,083 |
| 8 | UK.tw. | 39,574 |
| 9 | England.tw. | 28,590 |
| 10 | Wales.tw. | 7,966 |
| 11 | (Northern adj1 Ireland).tw. | 2,734 |
| 12 | Scotland.tw. | 5,771 |
| 13 | 8 or 9 or 10 or 11 or 12 | 75,467 |
| 14 | (Health adj1 expenditure).af. | 1,419 |
| 15 | (health adj2 costs).af. | 23,598 |
| 16 | (cost adj1 analysis).af. | 24,013 |
| 17 | (economic adj1 assessment).af. | 567 |
| 18 | (economic adj1 evaluation).af. | 10,577 |
| 19 | (economic adj1 implications).af. | 2,398 |
| 20 | (resource adj1 utilization).af. | 5,509 |
| 21 | (resource adj1 consumption).af. | 674 |
| 22 | (health adj1 care adj1 utilization).af. | 31,310 |
| 23 | (financial adj1 burden).af. | 1,961 |
| 24 | (financial adj1 stress).af. | 2,061 |
| 25 | (financial adj1 strain).af. | 7,321 |
| 26 | 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 | 93,920 |
| 27 | 7 and 13 and 26 | 116 |
| 28 | limit 27 to yr="2017 -Current" | 41 |
| 29 | limit 28 to ("300 adulthood " and "0110 peer-reviewed journal") | 37 |

# Appendix - Administrative Data Studies

### 6.C.1. Declarations and Supplementary Material paper 1

This paper and the supplementary material are available on BMJ Supportive and Palliative Care.

Download using:
https://spcare.bmj.com/content/bmjspcare/early/2021/02/11/bmjspcare-2020-002708.full.pdf

# Declarations paper 1

**Supplementary material: 3 Figures, 4 Tables**

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**Authorship**

JM and PH led the conception and design of the study. KD led the data acquisition, conducted data management and analysis supported by XL, EG, JM and PH. KD and EG led the data interpretation supported by XL, JB, EL, JM and PH. KD drafted and revised the article supported by JB and PH. All authors critically reviewed and edited the paper and approved the final version to be published.

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**Data sharing**

Data are not available for sharing via application to the Scottish Public Benefits and Privacy Panel.

**Competing Interest**

Competing Interest: None declared.

**Patient consent**

Not required

**Provenance and peer review**

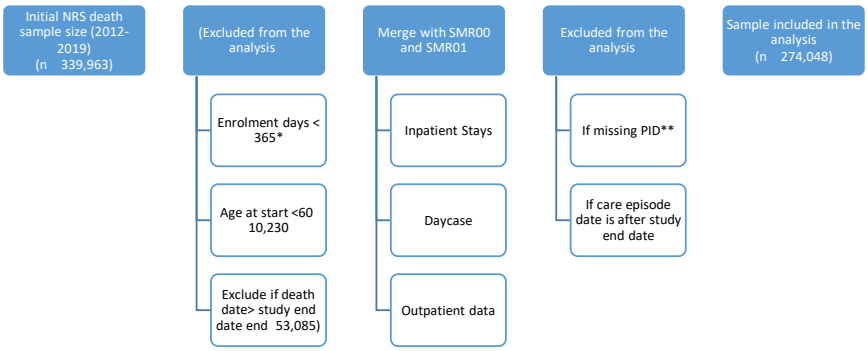
Not commissioned; externally peer reviewed.

**Licence for Publication**

# Supplementary Material paper 1

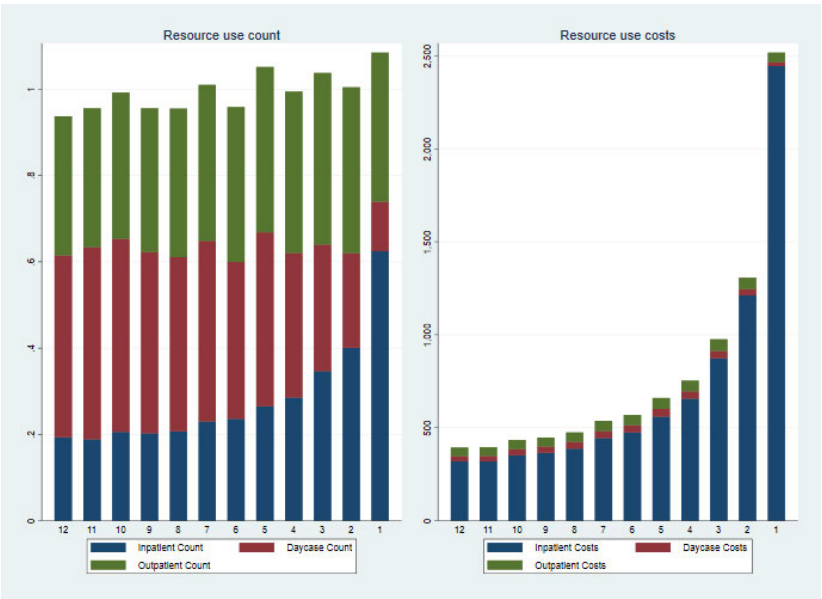
**Supplementary material: Healthcare use and cost trajectories during the last year of life: A national population administrative secondary care data linkage study**

*Supplementary figure S1: Flow chart of data linkage & inclusion/exclusion criteria*

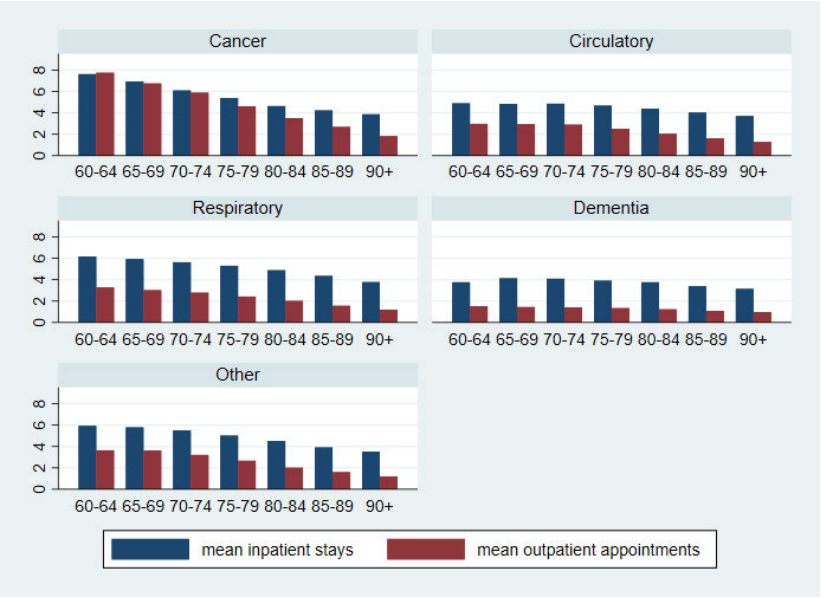



*Excluded if person died within 1 year from study start date of 1st Jan 2012
**PID = Person Identification Number

*Supplementary figure S2: Monthly health care utilisation and costs in the last 12 month*



*Supplementary figure S3: Average inpatient and outpatient count over age groups by cause of death*



*Supplementary table S1: Definitions of indices and methodological features*

| **Definitions** | |
|---|---|
| **SIMD** | SIMD is an index of multiple deprivation, measured at area (data zone) level and specific to Scotland. It is generated based on a combination of factors including combines seven different domains (aspects) of deprivation: income; employment; health; education, skills and training; geographic access to services; crime; and housing for small areas in Scotland. |
| **Community Health Index (CHI) number** | CHI Number: The Community Health Index (CHI) is a population register, which is used in Scotland for health care purposes. The CHI number is a unique 10-character numeric identifier, allocated to each patient on first registration and uniquely identifies a patient on the index. |
| **Overlapping and nested episodes** | Overlapping or nested episode: An episode of care is an inpatient episode, a day case episode, a day patient episode, a haemodialysis patient episode, an outpatient episode or an AHP episode. Each episode is initiated by a referral (including re-referral) or admission and is ended by a discharge. Overlapping or nested episodes comprise a series of service contacts as, for example, in an outpatient episode or a period of continuous contact as in an inpatient episode. It is important to note that a person may be in more than one episode at a time. |
| **Urban-rural Indicator** | 1. **Large Urban Areas**: Settlements of 125,000 or more people.<br>2. **Other Urban Areas**: Settlements of 10,000 to 124,999 people.<br>3. **Accessible Small Towns**: Settlements of 3,000 to 9,999 people and within 30 minutes' drive of a settlement of 10,000 or more.<br>4. **Remote Small Towns**: Settlements of 3,000 to 9,999 people and with a drive time of over 30 minutes to a settlement of 10,000 or more.<br>5. **Accessible Rural**: Areas with a population of less than 3,000 people, and within a 30 minute drive time of a settlement of 10,000 or more.<br>6. **Remote Rural:** Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a settlement of 10,000 or more. |

*Supplementary table S2: Frequency of Charlson score in each category*

| Charlson score | Frequency | Percent | Cum |
|---|---|---|---|
| **0** | 78,659 | 36.02 | 36.02 |
| **1** | 55,725 | 25.52 | 61.54 |
| **2** | 54,958 | 25.17 | 86.71 |
| **3** | 12,518 | 5.73 | 92.44 |
| **4** | 2,911 | 1.33 | 93.78 |
| **5** | 744 | 0.34 | 94.12 |
| **6** | 4,148 | 1.90 | 96.02 |
| **7** | 717 | 0.33 | 96.35 |
| **8** | 6,839 | 3.13 | 99.48 |
| **9** | 924 | 0.42 | 99.90 |
| **10** | 168 | 0.08 | 99.98 |
| **11** | 33 | 0.02 | 99.99 |
| **12** | 13 | 0.01 | 100.00 |
| **Total** | **218,357** | **100.00** | |
| **No score*** | *55,691* | | |

*Decedents without an inpatient appointment had no recorded CCI

*Supplementary table S3: Generalised linear model margins of 12 month costs (Log link)*

| | | Margin | Std Err | z | p | CI 95% | |
|---|---|---|---|---|---|---|---|
| **Age group** | 60-64 | 12411.49 | 71.68 | 173.15 | 0.00 | 12271.00 | 12551.98 |
| | 65-69 | 11894.10 | 60.43 | 196.83 | 0.00 | 11775.67 | 12012.54 |
| | 70-74 | 11615.50 | 50.99 | 227.78 | 0.00 | 11515.55 | 11715.44 |
| | 75-79 | 11331.65 | 46.39 | 244.25 | 0.00 | 11240.72 | 11422.58 |
| | 80-84 | 10970.34 | 47.64 | 230.28 | 0.00 | 10876.97 | 11063.71 |
| | 85-89 | 10499.62 | 56.54 | 185.69 | 0.00 | 10388.80 | 10610.44 |
| | 90+ | 10019.39 | 89.82 | 111.56 | 0.00 | 9843.35 | 10195.42 |
| | | | | | | | |
| **Gender** | Male | 11536.77 | 31.48 | 366.53 | 0.00 | 11475.08 | 11598.46 |
| | Female | 11234.95 | 29.80 | 377.04 | 0.00 | 11176.55 | 11293.35 |
| | | | | | | | |
| **Main Cause of Death** | Cancer | 10996.77 | 41.27 | 266.46 | 0.00 | 10915.88 | 11077.65 |
| | Circulatory | 10976.59 | 43.34 | 253.29 | 0.00 | 10891.66 | 11061.53 |
| | Respiratory | 11900.58 | 61.08 | 194.84 | 0.00 | 11780.87 | 12020.29 |
| | Dementia | 10713.53 | 88.99 | 120.39 | 0.00 | 10539.11 | 10887.94 |
| | Other | 12568.69 | 56.55 | 222.26 | 0.00 | 12457.85 | 12679.52 |
| | | | | | | | |
| **SIMD** | 1st | 11465.02 | 45.71 | 250.82 | 0.00 | 11375.43 | 11554.61 |
| | 2nd | 11504.83 | 44.95 | 255.97 | 0.00 | 11416.74 | 11592.92 |
| | 3rd | 11201.03 | 46.91 | 238.78 | 0.00 | 11109.09 | 11292.97 |
| | 4th | 11174.65 | 51.22 | 218.18 | 0.00 | 11074.27 | 11275.04 |
| | 5th | 11541.78 | 56.06 | 205.87 | 0.00 | 11431.90 | 11651.67 |
| | | | | | | | |
| **Rural/Urban** | Large Urban Areas | 12050.12 | 40.10 | 300.53 | 0.00 | 11971.53 | 12128.71 |
| | Other Urban Areas | 11283.67 | 35.69 | 316.17 | 0.00 | 11213.72 | 11353.61 |
| | Accessible Small Towns | 10891.06 | 66.23 | 164.44 | 0.00 | 10761.25 | 11020.87 |
| | Remote Small Towns | 10326.25 | 92.83 | 111.24 | 0.00 | 10144.31 | 10508.20 |
| | Accessible Rural | 10966.23 | 64.21 | 170.77 | 0.00 | 10840.37 | 11092.09 |
| | Remote Rural | 10553.03 | 79.61 | 132.56 | 0.00 | 10397.00 | 10709.06 |
| | | | | | | | |
| **Comorbidity Index** | 0 | 8384.87 | 28.33 | 295.93 | 0.00 | 8329.33 | 8440.40 |
| | 1 | 10727.13 | 42.76 | 250.89 | 0.00 | 10643.33 | 10810.93 |
| | 2 | 13831.01 | 58.59 | 236.05 | 0.00 | 13716.17 | 13945.85 |
| | 3 | 15578.73 | 122.46 | 127.21 | 0.00 | 15338.70 | 15818.75 |
| | 4 | 18402.42 | 296.20 | 62.13 | 0.00 | 17821.89 | 18982.96 |
| | 5 | 20308.35 | 646.38 | 31.42 | 0.00 | 19041.47 | 21575.22 |
| | 6 | 10701.59 | 147.40 | 72.60 | 0.00 | 10412.68 | 10990.50 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | 13499.78 | 438.19 | 30.81 | 0.00 | 12640.94 | 14358.62 |
| 8 | 18552.87 | 206.16 | 89.99 | 0.00 | 18148.80 | 18956.94 |
| 9 | 19651.49 | 564.13 | 34.84 | 0.00 | 18545.82 | 20757.16 |
| 10 | 20920.05 | 1398.38 | 14.96 | 0.00 | 18179.29 | 23660.82 |
| 11 | 18273.97 | 2754.05 | 6.64 | 0.00 | 12876.14 | 23671.80 |
| 12 | 27240.04 | 6540.17 | 4.17 | 0.00 | 14421.55 | 40058.53 |

*Supplementary table S4: Generalised linear model of monthly costs (Log link)*

| | exp(b) | Std. Err.* | z | p | 95% CI | |
|---|---|---|---|---|---|---|
| **Proximity to death** | reference group - one month | | | | | |
| **2** | 0.503 | 0.0025 | -136.160 | 0.000 | 0.498 | 0.508 |
| **3** | 0.373 | 0.0022 | -170.060 | 0.000 | 0.368 | 0.377 |
| **4** | 0.287 | 0.0018 | -193.770 | 0.000 | 0.284 | 0.291 |
| **5** | 0.250 | 0.0017 | -203.780 | 0.000 | 0.246 | 0.253 |
| **6** | 0.214 | 0.0015 | -215.410 | 0.000 | 0.211 | 0.217 |
| **7** | 0.202 | 0.0015 | -217.420 | 0.000 | 0.199 | 0.205 |
| **8** | 0.179 | 0.0014 | -224.060 | 0.000 | 0.176 | 0.182 |
| **9** | 0.168 | 0.0013 | -227.040 | 0.000 | 0.166 | 0.171 |
| **10** | 0.164 | 0.0013 | -227.170 | 0.000 | 0.161 | 0.166 |
| **11** | 0.149 | 0.0012 | -230.080 | 0.000 | 0.147 | 0.152 |
| **12** | 0.149 | 0.0012 | -228.700 | 0.000 | 0.147 | 0.152 |
| **Age group** | reference group - age group 60 to 64 | | | | | |
| **65-69** | 0.943 | 0.0098 | -5.610 | 0.000 | 0.924 | 0.963 |
| **70-74** | 0.914 | 0.0091 | -9.030 | 0.000 | 0.897 | 0.932 |
| **75-79** | 0.894 | 0.0087 | -11.490 | 0.000 | 0.877 | 0.911 |
| **80-84** | 0.874 | 0.0087 | -13.530 | 0.000 | 0.857 | 0.891 |
| **85-89** | 0.849 | 0.0092 | -15.100 | 0.000 | 0.831 | 0.867 |
| **90+** | 0.832 | 0.0116 | -13.140 | 0.000 | 0.810 | 0.855 |
| **Sex** | reference group - male | | | | | |
| **Female** | 0.980 | 0.0049 | -3.990 | 0.000 | 0.971 | 0.990 |
| **Main cause of death** | reference group - cancer | | | | | |
| **Circulatory** | 1.010 | 0.0077 | 1.260 | 0.207 | 0.995 | 1.025 |
| **Respiratory** | 1.091 | 0.0096 | 9.910 | 0.000 | 1.072 | 1.110 |
| **Dementia** | 1.109 | 0.0132 | 8.660 | 0.000 | 1.083 | 1.135 |
| **Other** | 1.141 | 0.0095 | 15.830 | 0.000 | 1.122 | 1.160 |
| **SIMD** | reference group - 1 (most deprived areas) | | | | | |
| **2nd** | 1.001 | 0.0073 | 0.100 | 0.918 | 0.987 | 1.015 |
| **3rd** | 0.970 | 0.0075 | -4.010 | 0.000 | 0.955 | 0.984 |
| **4th** | 0.981 | 0.0080 | -2.380 | 0.017 | 0.965 | 0.997 |
| **5th** | 1.012 | 0.0083 | 1.480 | 0.139 | 0.996 | 1.029 |
| **Rural Urban Indicator** | reference group - 1 (large urban areas) | | | | | |
| **2** | 0.920 | 0.0055 | -14.010 | 0.000 | 0.909 | 0.931 |
| **3** | 0.886 | 0.0080 | -13.370 | 0.000 | 0.870 | 0.902 |
| **4** | 0.827 | 0.0106 | -14.830 | 0.000 | 0.807 | 0.848 |
| **5** | 0.884 | 0.0080 | -13.580 | 0.000 | 0.869 | 0.900 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **6** | 0.855 | 0.0095 | -14.060 | 0.000 | 0.836 | 0.874 |
| | | | | | | |
| **Charlson Comorbidity Index** | reference group -0 (no comorbidities) | | | | | |
| **1** | 1.318 | 0.0089 | 41.040 | 0.000 | 1.301 | 1.336 |
| **2** | 1.778 | 0.0136 | 75.330 | 0.000 | 1.752 | 1.805 |
| **3** | 2.063 | 0.0211 | 70.780 | 0.000 | 2.022 | 2.105 |
| **4** | 2.536 | 0.0452 | 52.200 | 0.000 | 2.449 | 2.626 |
| **5** | 2.858 | 0.0955 | 31.430 | 0.000 | 2.677 | 3.052 |
| **6** | 1.226 | 0.0246 | 10.150 | 0.000 | 1.178 | 1.275 |
| **7** | 1.689 | 0.0649 | 13.650 | 0.000 | 1.566 | 1.821 |
| **8** | 2.490 | 0.0330 | 68.850 | 0.000 | 2.426 | 2.556 |
| **9** | 2.693 | 0.0758 | 35.180 | 0.000 | 2.548 | 2.846 |
| **10** | 2.974 | 0.1776 | 18.250 | 0.000 | 2.646 | 3.343 |
| **11** | 2.308 | 0.2837 | 6.800 | 0.000 | 1.814 | 2.937 |
| **12** | 4.081 | 0.7808 | 7.350 | 0.000 | 2.805 | 5.938 |
| | | | | | | |
| **cons** | **2527.635** | **30.5608** | **648.020** | **0.000** | **2468.44** | **2588.24** |
| *Std. Error – cluster | | | | | | |

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## 6.C.2. Declarations and Supplementary Material Cancer paper 2

This paper and the supplementary material are available on the 'preprint-server' MedRxiv.

Download using:

https://www.medrxiv.org/content/medrxiv/early/2022/03/03/2022.02.22.22271323.full.pdf

# Declarations paper 2

**Ethics**

Approval was granted by the Scottish Public Benefit and Privacy panel (Ref: 1617-0100) for analysis within the Scottish National Research Data Safe Haven.

**Patient consent and consent for publication**

Not required

**Data sharing**

Data are not available for sharing via application to the Scottish Public Benefits and Privacy Panel.

**Competing Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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This work was supported by the Health Foundation (www.health.org.uk). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Authors' contributions**

KD and led the conception and design of the study supported by PH. KD led the data acquisition, conducted data management and analysis supported by EL, EG, JM and PH. KD led the data interpretation supported by EG, EL, GT XL, JB, EL and PH. KD, EL, GT and JB drafted and revised the article supported PH. All authors critically reviewed and edited the paper and approved the final version to be published.

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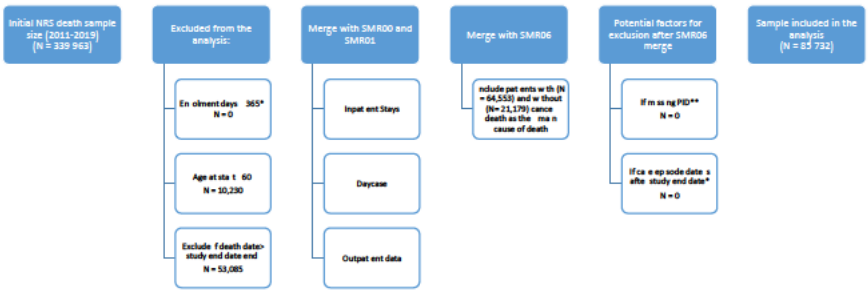
**Provenance and peer review**

Not commissioned; externally peer reviewed.

# Supplementary Material paper 2

**Supplementary material:** 7 Figures, 7 Tables

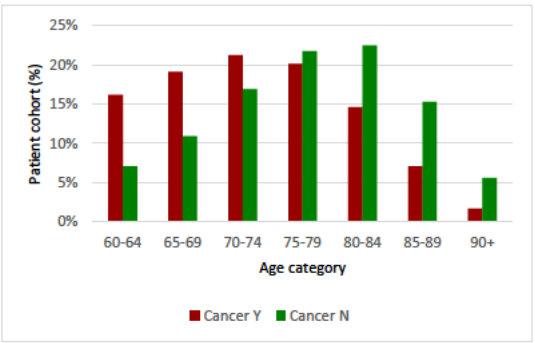
*Supplementary figure S1: Flow chart of data linkage & inclusion/exclusion criteria*




* No exclusions were necessary as the datasets included data for a longer time as the study period
**PID = Person Identification Number

NRS death: National Records of Scotland, Vital Events – Deaths; SMR00: Outpatient Attendance; SMR01: General/Acute Inpatient and Day Case; SMR06: Scottish Cancer Registry

*Supplementary figure S2: Percentage of cancer patients with cancer as their main cause of death (Cancer = Y) and "other" main death diagnosis (Cancer = N) by age*

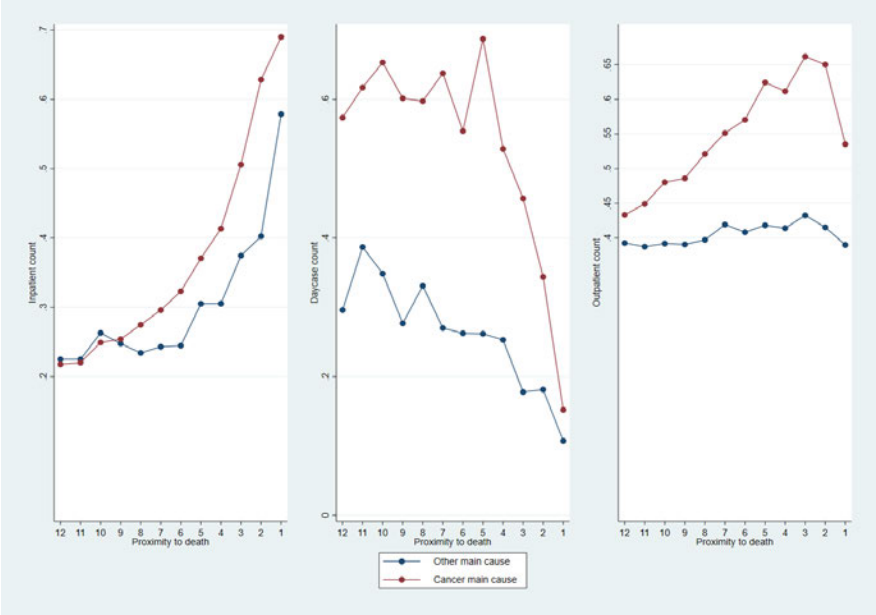


*Supplementary table 1: Resource use (Inpatient, Inpatient LOS, Outpatient appointments and day case use) over proximity to death (last 12, 6, 3, 1 month) by cancer type*

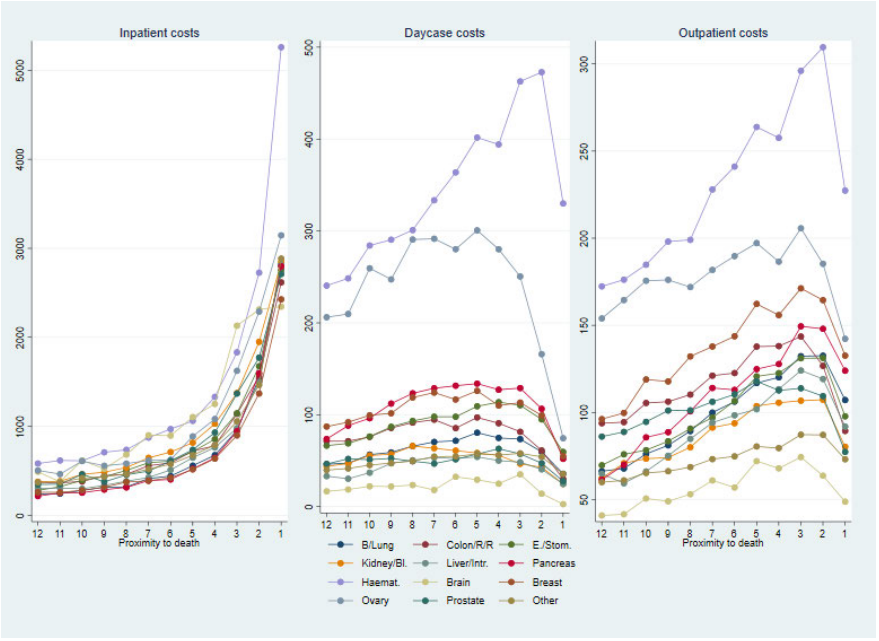
| | All | | Cancer main cause | | Bronchus Lung | | Col. Rect. Rectosig. | | Esoph. Stomache | | Liver Intrahep. | | Pancreas | | Kidney Bladder | | Breast | | Ovary | | Prostate | | Brain | | Haem. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| **Proximity to Death: 12 months** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inpatient | 5.88 | 5.68 | 5.99 | 5.88 | 5.30 | 4.11 | 5.75 | 4.68 | 6.15 | 4.93 | 5.21 | 4.41 | 5.68 | 5.60 | 6.36 | 4.57 | 5.60 | 5.19 | 8.41 | 8.33 | 5.72 | 4.23 | 5.27 | 3.42 | 11.80 | 14.99 |
| Average LOS | 7.15 | 13.14 | 7.10 | 12.54 | 6.52 | 11.38 | 7.36 | 13.02 | 6.09 | 10.69 | 7.78 | 12.03 | 6.96 | 10.74 | 7.88 | 13.90 | 8.29 | 16.12 | 6.72 | 12.67 | 7.94 | 13.14 | 9.07 | 15.58 | 6.10 | 12.09 |
| Outpatient | 5.01 | 6.00 | 5.31 | 6.28 | 5.08 | 5.04 | 5.09 | 6.35 | 4.97 | 4.64 | 4.29 | 4.65 | 4.78 | 5.86 | 4.86 | 5.00 | 6.25 | 7.34 | 6.59 | 7.08 | 5.24 | 5.14 | 3.94 | 3.87 | 9.92 | 14.31 |
| Day cases | 1.15 | 4.76 | 1.36 | 5.19 | 0.97 | 3.19 | 1.19 | 3.89 | 1.45 | 4.33 | 0.64 | 2.85 | 1.52 | 5.07 | 0.92 | 3.37 | 1.40 | 4.61 | 3.20 | 8.18 | 0.83 | 2.92 | 0.30 | 1.73 | 6.45 | 15.33 |
| **Proximity to Death: 6 months** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inpatient | 3.47 | 3.70 | 3.55 | 3.77 | 3.40 | 3.12 | 3.20 | 3.20 | 3.55 | 3.42 | 3.32 | 3.15 | 3.48 | 3.44 | 3.64 | 3.39 | 3.15 | 3.33 | 4.07 | 4.84 | 3.37 | 3.38 | 3.49 | 2.98 | 6.01 | 8.32 |
| Average LOS | 7.56 | 12.31 | 7.63 | 11.98 | 7.02 | 11.07 | 8.04 | 13.02 | 6.80 | 11.16 | 8.26 | 12.14 | 7.37 | 10.40 | 8.54 | 13.13 | 8.74 | 12.84 | 7.69 | 11.35 | 8.75 | 13.56 | 9.53 | 14.42 | 6.44 | 12.10 |
| Outpatient | 2.79 | 3.52 | 3.01 | 3.69 | 2.98 | 3.07 | 2.77 | 3.67 | 2.83 | 2.85 | 2.47 | 2.90 | 2.84 | 3.54 | 2.69 | 2.92 | 3.48 | 4.26 | 3.42 | 4.11 | 2.72 | 3.01 | 2.21 | 2.27 | 5.67 | 8.26 |
| Day cases | 0.47 | 2.45 | 0.56 | 2.68 | 0.44 | 1.84 | 0.43 | 1.88 | 0.63 | 2.28 | 0.28 | 1.65 | 0.64 | 2.63 | 0.35 | 1.69 | 0.50 | 2.25 | 1.12 | 4.08 | 0.30 | 1.57 | 0.12 | 0.91 | 2.73 | 7.99 |
| **Proximity to Death: 3 months** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inpatient | 2.05 | 2.50 | 2.08 | 2.50 | 2.11 | 2.31 | 1.85 | 2.28 | 2.00 | 2.45 | 2.02 | 2.32 | 2.09 | 2.31 | 2.03 | 2.45 | 1.85 | 2.24 | 2.07 | 2.67 | 1.89 | 2.39 | 1.94 | 2.36 | 2.98 | 4.40 |
| Average LOS | 7.67 | 11.05 | 7.91 | 11.00 | 7.33 | 10.27 | 8.24 | 11.26 | 7.33 | 10.46 | 8.29 | 10.91 | 7.62 | 10.03 | 8.85 | 12.16 | 9.19 | 12.19 | 8.29 | 10.41 | 9.09 | 12.38 | 10.68 | 14.13 | 6.38 | 10.43 |
| Outpatient | 1.19 | 1.22 | 1.28 | 1.24 | 1.34 | 1.20 | 1.13 | 1.20 | 1.25 | 1.19 | 1.12 | 1.15 | 1.27 | 1.24 | 1.17 | 1.15 | 1.38 | 1.31 | 1.40 | 1.25 | 1.12 | 1.17 | 1.01 | 1.06 | 1.82 | 1.66 |
| Day cases | 0.17 | 1.13 | 0.19 | 1.24 | 0.16 | 0.91 | 0.14 | 0.90 | 0.24 | 1.16 | 0.11 | 0.92 | 0.23 | 1.24 | 0.12 | 0.81 | 0.17 | 1.09 | 0.31 | 1.64 | 0.09 | 0.67 | 0.03 | 0.37 | 0.98 | 3.72 |
| Proximity to Death: 1 month | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inpatient | 0.79 | 1.39 | 0.76 | 1.35 | 0.82 | 1.38 | 0.66 | 1.27 | 0.67 | 1.28 | 0.80 | 1.34 | 0.74 | 1.26 | 0.63 | 1.30 | 0.73 | 1.29 | 0.63 | 1.26 | 0.63 | 1.22 | 0.46 | 1.15 | 0.90 | 1.63 |
| Average LOS | 6.01 | 6.83 | 6.45 | 7.00 | 6.14 | 6.77 | 6.60 | 7.12 | 6.33 | 6.85 | 6.66 | 7.18 | 6.66 | 7.03 | 6.88 | 6.97 | 6.64 | 7.02 | 7.33 | 7.45 | 6.98 | 7.37 | 7.98 | 8.13 | 5.26 | 6.51 |
| Outpatient | 0.46 | 0.85 | 0.50 | 0.88 | 0.52 | 0.84 | 0.41 | 0.77 | 0.46 | 0.80 | 0.43 | 0.78 | 0.53 | 0.96 | 0.43 | 0.76 | 0.56 | 0.92 | 0.56 | 0.97 | 0.39 | 0.74 | 0.37 | 0.76 | 0.87 | 1.47 |
| Day cases | 0.03 | 0.33 | 0.03 | 0.34 | 0.03 | 0.30 | 0.02 | 0.22 | 0.04 | 0.37 | 0.02 | 0.28 | 0.03 | 0.34 | 0.02 | 0.21 | 0.03 | 0.31 | 0.03 | 0.34 | 0.02 | 0.25 | 0.00 | 0.00 | 0.12 | 0.77 |

LOS: Length of stay

*Supplementary Figure 3: Inpatient, day case and outpatient resource use patterns in cancer- patients' last 12 months of life. Proximity to death (in month) on the x-axis; average resource use within each month on the y-axis. Results are presented for cancer patients with and without cancer as main cause of death.*



*death (in month) on the x-axis; average costs (in £) within each month on the y-axis. Results are presented for each cancer type.*




Other main: cancer not main cause of death; Bronchus/L: Bronchus and Lung cancer; Colon/R/R: Colon, Rectosigmoideum and Rectum cancer; Esoph/Sto.: Esophagus/Stomach; Liver/Intra.: Liver and Intrahepatic cancer; Kidney/Bl.: Kidney and Bladder cancer; Hemat.: Hematologic cancer

| Sex | Costs | CI [95%} |
|---|---|---|
| Male | 12562.7*** | [12451.7,12673.7] |
| Female | 11616.0*** | [11508.5,11723.5] |
| Observations | 85328 | |

* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary table 3: Univariate Analysis GLM - Age in categories*

| Age category | Costs | CI [95%] |
|---|---|---|
| 60-64 | 15895.0*** | [15632.4,16157.5] |
| 65-69 | 14216.6*** | [14004.5,14428.8] |
| 70-74 | 12708.3*** | [12533.8,12882.8] |
| 75-79 | 11212.3*** | [11059.6,11365.0] |
| 80-84 | 9765.3*** | [9617.2,9913.5] |
| 85-89 | 8583.4*** | [8407.8,8759.0] |
| 90+ | 7738.8*** | [7444.4,8033.3] |
| Observations | 85328 | |

* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary table 4: Univariate Analysis GLM – Cancer type (grouped)*

| Cancer type/ group | Costs | CI [95%] |
|---|---|---|
| Cancer NOT main cause † | 10532.4*** | [10402.3,10662.5] |
| Bronchus/Lung | 10812.5*** | [10669.2,10955.8] |
| Colon/Rectosig/Rectum | 12395.4*** | [12115.5,12675.3] |
| Esoph./Stomache | 12639.3*** | [12334.3,12944.2] |
| Kidney/Bladder | 13347.2*** | [12945.2,13749.3] |
| Liver/Intrahepatic | 10947.7*** | [10546.6,11348.8] |
| Pancreas | 11312.9*** | [10961.0,11664.7] |
| Haematologic | 24358.4*** | [23454.2,25262.7] |
| Brain | 14617.4*** | [13846.4,15388.4] |
| Breast | 11089.2*** | [10656.2,11522.3] |
| Ovary | 18070.3*** | [17179.4,18961.3] |
| Prostate | 12501.9*** | [12081.0,12922.8] |
| Other cancers | 13114.2*** | [12922.6,13305.8] |
| Observations | 85328 | |

* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary table 5: Univariate Analysis GLM - Comorbidity (Charlson score 0 to 12)*

| Charlson Comorbidity Index | Costs | CI [95%] |
|---|---|---|
| 0 | 9221.5*** | [9086.7,9356.3] |
| 1 | 11735.3*** | [11498.0,11972.6] |
| 2 | 13287.1*** | [13171.3,13403.0] |
| 3 | 15167.7*** | [14886.0,15449.4] |
| 4 | 18513.3*** | [17736.1,19290.6] |
| 5 | 19746.4*** | [18124.5,21368.2] |
| 6 | 9608.1*** | [9313.8,9902.4] |
| 7 | 13239.1*** | [12293.6,14184.7] |
| 8 | 18177.0*** | [17755.0,18598.9] |
| 9 | 19455.4*** | [18254.7,20656.1] |
| 10 | 21071.9*** | [18012.9,24130.9] |
| 11 | 18674.2*** | [12057.9,25290.6] |
| 12 | 22770.0*** | [10535.0,35005.0] |
| Observations | 78919 | |

* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary table 6: Univariate Analysis GLM - Rural-Urban Indicator*

| Urban-rural indicator | Costs | CI [95%] |
|---|---|---|
| Large urban area | 12605.0*** | [12484.1,12725.9] |
| Other Urban Areas | 11867.5*** | [11740.0,11995.0] |
| Accessible Small Towns | 11717.2*** | [11475.1,11959.2] |
| Remote Small Towns | 11194.5*** | [10753.3,11635.7] |
| Accessible Rural Areas | 11005.1*** | [10431.8,11578.4] |
| Remote Rural Areas | 11296.5*** | [11017.6,11575.4] |
| Observations | 85328 | |

* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary table 7: Univariate Analysis GLM - SIMD*

| Scottish Index of Multiple Deprivation | Costs | CI [95%] |
|---|---|---|
| 1st (most deprived) | 12252.7*** | [12088.3,12417.1] |
| 2nd | 12052.0*** | [11891.3,12212.7] |
| 3rd | 11815.1*** | [11649.9,11980.4] |
| 4th | 11876.8*** | [11697.1,12056.5] |
| 5th | 12645.7*** | [12442.0,12849.4] |
| Observations | 85238 | |

* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary table 8: Multivariate Analysis GLM - Cancer MAIN cause of death*

| Age category | Coefficient | CI [95%] |
|---|---|---|
| 60-64 | 0 | [0,0] |
| 65-69 | -0.0991*** | [-0.126,-0.0717] |
| 70-74 | -0.203*** | [-0.241,-0.165] |
| 75-79 | -0.301*** | [-0.352,-0.250] |
| 80-84 | -0.419*** | [-0.484,-0.353] |
| 85-89 | -0.484*** | [-0.565,-0.402] |
| 90+ | -0.529*** | [-0.635,-0.422] |
| Comorbidity Index category | | |
| CCI 0 | 0 | [0,0] |
| CCI 1 | 0.302*** | [0.266,0.339] |
| CCI 2 | 0.187*** | [0.109,0.266] |
| CCI 3 | 0.488*** | [0.371,0.604] |
| Age and Comorbidity | | |
| age at death | 0.00434* | [0.00100,0.00768] |
| Charlson (0-12) | 0.0752*** | [0.0382,0.112] |
| age # Charlson | -0.000866*** | [-0.00130,-0.000435] |
| Sex | | |
| Male | 0 | [0,0] |
| Female | -0.0366*** | [-0.0502,-0.0230] |
| Scottish Index of Multiple Deprivation | | |
| 1st (most deprived) | 0 | [0,0] |
| 2nd | 0.00811 | [-0.0119,0.0281] |
| 3rd | 0.0216* | [0.000498,0.0426] |
| 4th | 0.0358** | [0.0141,0.0575] |
| 5th | 0.0983*** | [0.0760,0.121] |
| Urban-rural indicator | | |
| RU 1 | 0 | [0,0] |
| RU 2 | -0.0521*** | [-0.0675,-0.0367] |
| RU 3 | -0.0777*** | [-0.102,-0.0535] |
| RU 4 | -0.0914*** | [-0.135,-0.0480] |
| RU 5 | -0.0996*** | [-0.156,-0.0437] |
| RU 6 | -0.0789*** | [-0.108,-0.0501] |
| Constant | 9.080*** | [8.844,9.316] |
| Observations | 60728 | |

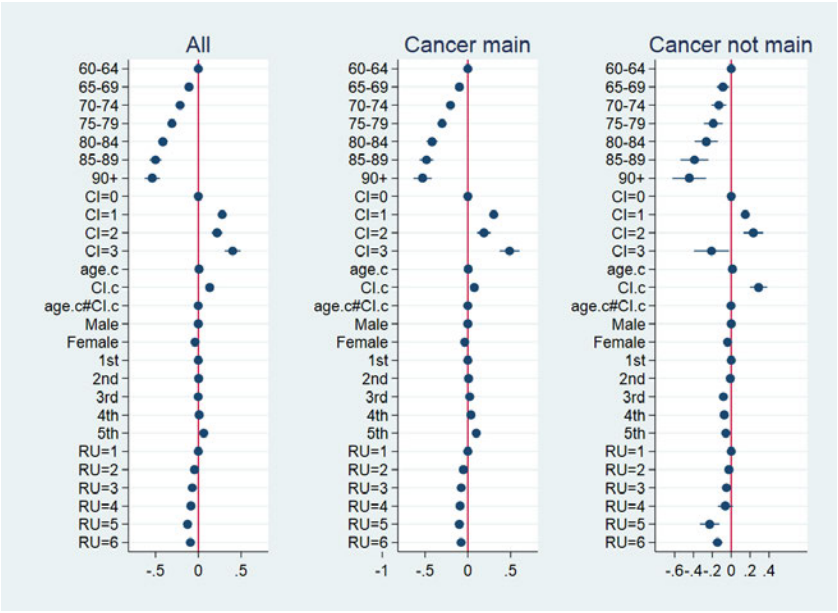
* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary table 9: Multivariate Analysis GLM - Cancer NOT main cause of death*

| Age category | Coefficient | CI [95%] |
|---|---|---|
| 60-64 | 0 | [0,0] |
| 65-69 | -0.0880** | [-0.153,-0.0235] |
| 70-74 | -0.132** | [-0.210,-0.0528] |
| 75-79 | -0.191*** | [-0.291,-0.0902] |
| 80-84 | -0.264*** | [-0.387,-0.141] |
| 85-89 | -0.390*** | [-0.538,-0.241] |
| 90+ | -0.445*** | [-0.624,-0.266] |
| Comorbidity Index category | | |
| CCI 0 | 0 | [0,0] |
| CCI 1 | 0.149*** | [0.105,0.193] |
| CCI 2 | 0.235*** | [0.130,0.339] |
| CCI 3 | -0.209* | [-0.395,-0.0230] |
| Age and Comorbidity | | |
| age at death | 0.0130*** | [0.00716,0.0189] |
| charlson (0-12) | 0.290*** | [0.198,0.382] |
| age # charlson | -0.00250*** | [-0.00361,-0.00140] |
| Sex | | |
| Male | 0 | [0,0] |
| Female | -0.0386** | [-0.0633,-0.0138] |
| Scottish Index of Multiple Deprivation | | |
| 1st | 0 | [0,0] |
| 2nd | -0.00966 | [-0.0461,0.0268] |
| 3rd | -0.0826*** | [-0.120,-0.0448] |
| 4th | -0.0741*** | [-0.113,-0.0348] |
| 5th | -0.0573** | [-0.0976,-0.0170] |
| Urban-rural indicator | | |
| RU 1 | 0 | [0,0] |
| RU 2 | -0.0247 | [-0.0523,0.00283] |
| RU 3 | -0.0502* | [-0.0939,-0.00659] |
| RU 4 | -0.0625 | [-0.141,0.0161] |
| RU 5 | -0.229*** | [-0.332,-0.125] |
| RU 6 | -0.145*** | [-0.199,-0.0921] |
| Constant | 8.377*** | [7.962,8.792] |
| Observations | 18093 | |

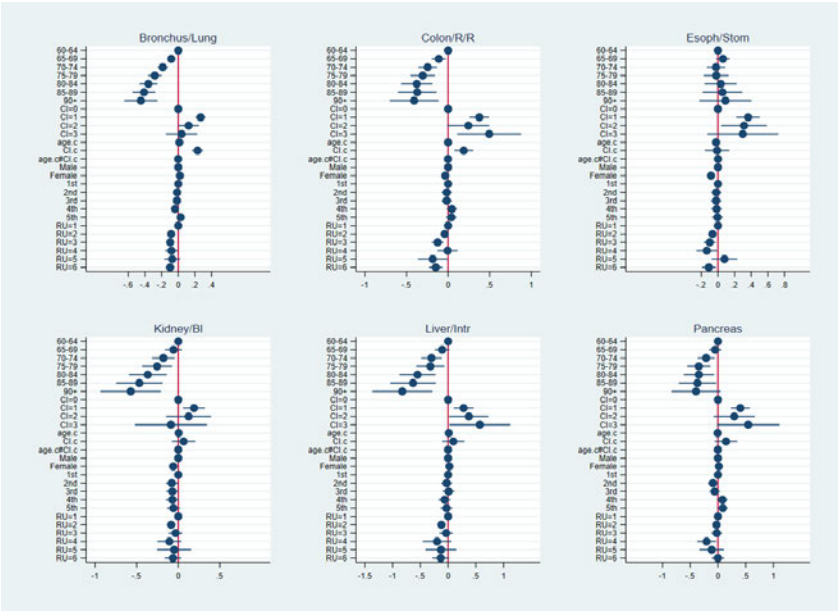
* p < 0.05, ** p < 0.01, *** p < 0.001

*Supplementary figure 5: Graphical representation of GLM results including interaction term (interaction between age and comorbidity burden) for all patients, and those with and without cancer as main cause of death*



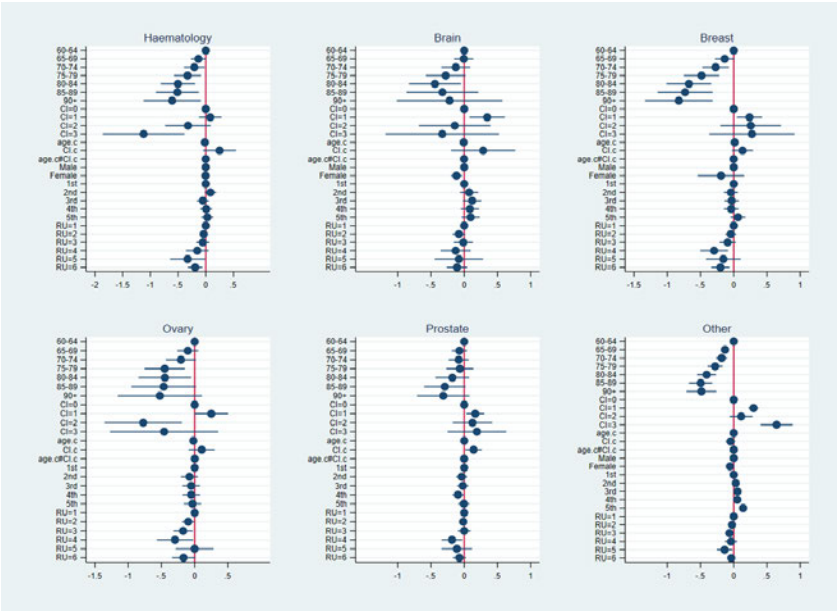

CI: Charlson Comorbidity Index; age.c: Age as a continuous variable; CI.c: Charlson Comorbidity Index as a continuous variable; age.c#CI.c: Interaction between age and Charlson Comorbidity Index (both as continuous variables); 1st to 5th: SIMD1 to SIMD 5 (Scottish index of multiple deprivation) in quintiles from most to least deprived areas; RU: Urban-rural indicator

*Supplementary figure 6: Graphical representation of GLM results including interaction term (interaction between age and comorbidity burden) for the different cancer types 1/2*




CI: Charlson Comorbidity Index; age.c: Age as a continuous variable; CI.c: Charlson Comorbidity Index as a continuous variable; age.c#CI.c: Interaction between age and Charlson Comorbidity Index (both as continuous variables); 1st to 5th: SIMD1 to SIMD 5 (Scottish index of multiple deprivation) in quintiles from most to least deprived areas; RU: Urban-rural indicator

*Supplementary figure 7: Graphical representation of GLM results including interaction term (interaction between age and comorbidity burden) for the different cancer types 2/2*




CI: Charlson Comorbidity Index; age.c: Age as a continuous variable; CI.c: Charlson Comorbidity Index as a continuous variable; age.c#CI.c: Interaction between age and Charlson Comorbidity Index (both as continuous variables); 1st to 5th: SIMD1 to SIMD 5 (Scottish index of multiple deprivation) in quintiles from most to least deprived areas; RU: Urban-rural indicator

*Table 10: GLM results for decedents with cancer as their main cause of death and cancer not as their main cause and for individual cancer types*

| | Cancer main | | Cancer not main | | Bronchus/Lung | | Colon/R/Rectum | | Esoph/Stomache | | Kidney/Bladder | | Liver/Intrahep. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age category | | | | | | | | | | | | | | |
| 60-64 | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| 65-69 | -0.0991*** | [-0.126,-0.0717] | -0.0880** | [-0.153,-0.0235] | -0.0844*** | [-0.127,-0.0418] | -0.112** | [-0.196,-0.0286] | 0.0599 | [-0.0209,0.141] | -0.0578 | [-0.160,0.0443] | -0.107 | [-0.239,0.0249] |
| 70-74 | -0.203*** | [-0.241,-0.165] | -0.132** | [-0.210,-0.0528] | -0.186*** | [-0.247,-0.125] | -0.246*** | [-0.358,-0.133] | -0.0237 | [-0.134,0.0865] | -0.179* | [-0.316,-0.0428] | -0.300** | [-0.484,-0.117] |
| 75-79 | -0.301*** | [-0.352,-0.250] | -0.191*** | [-0.291,-0.0902] | -0.282*** | [-0.365,-0.199] | -0.305*** | [-0.454,-0.157] | -0.0209 | [-0.170,0.128] | -0.255** | [-0.435,-0.0747] | -0.320* | [-0.573,-0.0664] |
| 80-84 | -0.419*** | [-0.484,-0.353] | -0.264*** | [-0.387,-0.141] | -0.359*** | [-0.466,-0.253] | -0.377*** | [-0.565,-0.190] | 0.0335 | [-0.160,0.227] | -0.366** | [-0.594,-0.139] | -0.552*** | [-0.877,-0.227] |
| 85-89 | -0.484*** | [-0.565,-0.402] | -0.390*** | [-0.538,-0.241] | -0.412*** | [-0.548,-0.276] | -0.371** | [-0.602,-0.140] | 0.0542 | [-0.184,0.293] | -0.468** | [-0.748,-0.189] | -0.633** | [-1.044,-0.222] |
| 90+ | -0.529*** | [-0.635,-0.422] | -0.445*** | [-0.624,-0.266] | -0.449*** | [-0.649,-0.250] | -0.408** | [-0.703,-0.114] | 0.0893 | [-0.223,0.402] | -0.572** | [-0.935,-0.208] | -0.827** | [-1.368,-0.285] |
| Comorbidity category | | | | | | | | | | | | | | |
| CCI 0 | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| CCI 1 (1 to 3) | 0.302*** | [0.266,0.339] | 0.149*** | [0.105,0.193] | 0.268*** | [0.208,0.329] | 0.375*** | [0.258,0.493] | 0.362*** | [0.221,0.504] | 0.189** | [0.0577,0.321] | 0.279** | [0.101,0.458] |
| CCI 2 (4 to 6) | 0.187*** | [0.109,0.266] | 0.235*** | [0.130,0.339] | 0.124* | [0.00170,0.246] | 0.243 | [-0.00980,0.496] | 0.313* | [0.0383,0.588] | 0.124 | [-0.146,0.395] | 0.373* | [0.0186,0.728] |
| CCI 3 (7 to 12) | 0.488*** | [0.371,0.604] | -0.209* | [-0.395,-0.0230] | 0.0394 | [-0.149,0.228] | 0.494* | [0.110,0.878] | 0.298 | [-0.129,0.726] | -0.0884 | [-0.522,0.345] | 0.572* | [0.0243,1.119] |
| Age, comorbidity index (0 to 12) and interaction between age and comorbidity | | | | | | | | | | | | | | |
| age at death | 0.00434* | [0.00100,0.00768] | 0.0130*** | [0.00716,0.0189] | 0.0128*** | [0.00724,0.0184] | -0.000326 | [-0.0098,0.0092] | -0.0231*** | [-0.0333,-0.0128] | 0.00498 | [-0.0066,0.0166] | 0.0131 | [-0.0041,0.0304] |
| charlson (0-12) | 0.0752*** | [0.0382,0.112] | 0.290*** | [0.198,0.382] | 0.232*** | [0.167,0.297] | 0.188** | [0.0741,0.301] | -0.0108 | [-0.157,0.135] | 0.0645 | [-0.0760,0.205] | 0.0937 | [-0.107,0.294] |
| age # charlson | -0.000866*** | [-0.0013,-0.0004] | -0.00250*** | [-0.0036,-0.001] | -0.00181*** | [-0.0025,-0.001] | -0.00194** | [-0.0032,-0.0006] | 0.000742 | [-0.00099,0.0024] | 0.000274 | [-0.0013,0.0018] | -0.000913 | [-0.0034,0.0015] |
| Sex | | | | | | | | | | | | | | |
| Male | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| Female | -0.0366*** | [-0.0502,-0.0230] | -0.0386** | [-0.063,-0.0138] | 0.02 | [-0.0024,0.0425] | -0.035 | [-0.0741,0.0040] | -0.0835*** | [-0.125,-0.0418] | -0.0604* | [-0.108,-0.0125] | 0.0222 | [-0.0464,0.0909] |
| Scottish Index of Multiple Deprivation (SIMD) | | | | | | | | | | | | | | |
| 1st | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| 2nd | 0.00811 | [-0.0119,0.0281] | -0.00966 | [-0.0461,0.0268] | -0.0145 | [-0.0449,0.0160] | -0.0168 | [-0.0772,0.0436] | -0.021 | [-0.0810,0.0389] | -0.0780* | [-0.148,-0.00798] | -0.0262 | [-0.124,0.0719] |
| 3rd | 0.0216* | [0.000498,0.0426] | -0.0826*** | [-0.120,-0.0448] | -0.0166 | [-0.0504,0.0171] | -0.0167 | [-0.0783,0.0449] | -0.0222 | [-0.0848,0.0404] | -0.0713 | [-0.145,0.00206] | 0.00838 | [-0.0962,0.113] |
| 4th | 0.0358** | [0.0141,0.0575] | -0.0741*** | [-0.113,-0.0348] | -0.0387* | [-0.075,-0.0024] | 0.0449 | [-0.0171,0.107] | -0.016 | [-0.0801,0.0481] | -0.0705 | [-0.147,0.00602] | -0.0632 | [-0.168,0.0417] |
| 5th | 0.0983*** | [0.0760,0.121] | -0.0573** | [-0.097,-0.0170] | 0.0283 | [-0.0117,0.0683] | 0.0383 | [-0.0248,0.101] | -0.00544 | [-0.0709,0.0600] | -0.0584 | [-0.136,0.0189] | -0.0302 | [-0.137,0.0765] |
| Urban- rural indicator | | | | | | | | | | | | | | |
| RU 1 | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| RU 2 | -0.0521*** | [-0.0675,-0.0367] | -0.0247 | [-0.052,0.00283] | -0.0856*** | [-0.111,-0.0604] | -0.0409 | [-0.085,0.00347] | -0.0652** | [-0.111,-0.0195] | -0.0854** | [-0.139,-0.0322] | -0.121** | [-0.196,-0.0461] |
| RU 3 | -0.0777*** | [-0.102,-0.0535] | -0.0502* | [-0.094,-0.0066] | -0.0966*** | [-0.137,-0.0565] | -0.126*** | [-0.195,-0.0569] | -0.0990** | [-0.168,-0.0298] | -0.0327 | [-0.115,0.0492] | -0.0355 | [-0.156,0.0846] |
| RU 4 | -0.0914*** | [-0.135,-0.0480] | -0.0625 | [-0.141,0.0161] | -0.0822* | [-0.158,-0.0063] | -0.00631 | [-0.128,0.115] | -0.134* | [-0.258,-0.0109] | -0.107 | [-0.251,0.0364] | -0.199 | [-0.457,0.0584] |
| RU 5 | -0.0996*** | [-0.156,-0.0437] | -0.229*** | [-0.332,-0.125] | -0.0728 | [-0.167,0.0216] | -0.185* | [-0.363,-0.00761] | 0.0781 | [-0.0764,0.233] | -0.0499 | [-0.255,0.155] | -0.129 | [-0.406,0.148] |
| RU 6 | -0.0789*** | [-0.108,-0.0501] | -0.145*** | [-0.199,-0.0921] | -0.0980*** | [-0.151,-0.0450] | -0.148*** | [-0.228,-0.0683] | -0.110** | [-0.193,-0.0264] | -0.0637 | [-0.163,0.0354] | -0.133 | [-0.283,0.0178] |
| Constant | 9.080 | [8.844,9.316] | 8.377 | [7.962,8.792] | 8.090 | [7.698,8.482] | 9.308 | [8.626,9.989] | 10.88 | [10.14,11.62] | 9.091 | [8.263,9.918] | 8.287 | [7.061,9.512] |
| Observations | 60728 | | 18093 | | 17345 | | 5938 | | 5364 | | 3407 | | 2288 | |

95% confidence intervals in brackets
* p < 0.05, ** p < 0.01, *** p < 0.001

| | Pancreas | | Hematologic | | Brain | | Breast | | Ovary | | Prostate | | "other" cancer | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age category | | | | | | | | | | | | | | |
| 60-64 | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| 65-69 | -0.0506 | [-0.160,0.0589] | -0.133 | [-0.270,0.00376] | -0.00586 | [-0.151,0.140] | -0.136 | [-0.283,0.0109] | -0.104 | [-0.262,0.0555] | -0.0725 | [-0.188,0.0428] | -0.131*** | [-0.193,-0.0694] |
| 70-74 | -0.213** | [-0.367,-0.0591] | -0.206* | [-0.392,-0.0206] | -0.127 | [-0.342,0.0881] | -0.272** | [-0.471,-0.0739] | -0.207 | [-0.431,0.0178] | -0.0825 | [-0.235,0.0698] | -0.181*** | [-0.265,-0.0982] |
| 75-79 | -0.346** | [-0.556,-0.137] | -0.329** | [-0.572,-0.0855] | -0.279 | [-0.577,0.0198] | -0.484*** | [-0.749,-0.218] | -0.451** | [-0.755,-0.147] | -0.0651 | [-0.269,0.139] | -0.280*** | [-0.392,-0.167] |
| 80-84 | -0.344* | [-0.618,-0.0705] | -0.503** | [-0.812,-0.193] | -0.441* | [-0.830,-0.0512] | -0.674*** | [-1.011,-0.338] | -0.448* | [-0.843,-0.0530] | -0.178 | [-0.432,0.0758] | -0.408*** | [-0.550,-0.265] |
| 85-89 | -0.369* | [-0.707,-0.0314] | -0.513** | [-0.899,-0.126] | -0.328 | [-0.868,0.213] | -0.732*** | [-1.146,-0.318] | -0.466 | [-0.952,0.0199] | -0.292 | [-0.603,0.0197] | -0.497*** | [-0.673,-0.322] |
| 90+ | -0.395 | [-0.837,0.0467] | -0.607* | [-1.125,-0.0892] | -0.22 | [-1.015,0.574] | -0.826** | [-1.336,-0.316] | -0.524 | [-1.159,0.111] | -0.315 | [-0.709,0.0798] | -0.486*** | [-0.712,-0.260] |
| Comorbidity category | | | | | | | | | | | | | | |
| CCI 0 | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| CCI 1 | 0.404*** | [0.233,0.575] | 0.0807 | [-0.124,0.285] | 0.346* | [0.0787,0.613] | 0.238* | [0.0474,0.428] | 0.249 | [-0.00356,0.502] | 0.167* | [0.0328,0.300] | 0.298*** | [0.226,0.371] |
| CCI 2 | 0.294 | [-0.0770,0.665] | -0.321 | [-0.732,0.0908] | -0.141 | [-0.681,0.398] | 0.256 | [-0.199,0.711] | -0.774** | [-1.356,-0.191] | 0.124 | [-0.174,0.423] | 0.112 | [-0.061,0.285] |
| CCI 3 | 0.545 | [-0.0173,1.108] | -1.123** | [-1.860,-0.385] | -0.33 | [-1.183,0.524] | 0.274 | [-0.368,0.916] | -0.459 | [-1.272,0.354] | 0.191 | [-0.251,0.634] | 0.645*** | [0.404,0.886] |
| Age, comorbidity index (0 to 12) and interaction between age and comorbidity | | | | | | | | | | | | | | |
| age at death | -0.00572 | [-0.0199,0.00844] | -0.0166* | [-0.0329,-0.0003] | -0.00745 | [-0.0305,0.0156] | 0.0154 | [-0.000103,0.0319] | -0.0196 | [-0.0397,0.0005] | 0.000266 | [-0.0127,0.0132] | -0.00043 | [-0.00762,0.006676] |
| charlson (0-12) | 0.145 | [-0.0579,0.348] | 0.249 | [-0.0486,0.547] | 0.285 | [-0.198,0.769] | 0.133 | [-0.0257,0.291] | 0.106 | [-0.0898,0.302] | 0.141* | [0.0169,0.266] | -0.0474 | [-0.117,0.0222] |
| age # charlson | -0.00159 | [-0.0040,0.00081] | -0.000618 | [-0.0041,0.0029] | -0.00226 | [-0.0084,0.0038] | -0.00124 | [-0.0029,0.00044] | 0.000899 | [-0.0011,0.0029] | -0.00119 | [-0.0025,0.00022] | 0.000000274 | [-0.00078,0.00079] |
| Sex | | | | | | | | | | | | | | |
| Male | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | NA | NA | 0 | [0,0] | 0 | [0,0] |
| Female | 0.0157 | [-0.0410,0.0723] | -0.00366 | [-0.0697,0.0624] | -0.116** | [-0.198,-0.0344] | -0.191 | [-0.542,0.160] | 0 | [0,0] | NA | NA | -0.0559*** | [-0.0854,-0.0263] |
| Scottish Index of Multiple Deprivation (SIMD) | | | | | | | | | | | | | | |
| 1st | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| 2nd | -0.0905* | [-0.178,-0.00292] | 0.0849 | [-0.0191,0.189] | 0.0746 | [-0.0622,0.211] | -0.0427 | [-0.149,0.0634] | -0.0786 | [-0.207,0.0497] | -0.038 | [-0.121,0.0453] | 0.03 | [-0.0141,0.0742] |
| 3rd | -0.0592 | [-0.150,0.0313] | -0.0521 | [-0.159,0.0551] | 0.12 | [-0.0191,0.259] | -0.0314 | [-0.140,0.0774] | -0.053 | [-0.185,0.0790] | -0.0208 | [-0.106,0.0645] | 0.0568* | [0.0112,0.102] |
| 4th | 0.0809 | [-0.0104,0.172] | 0.00797 | [-0.0990,0.115] | 0.0851 | [-0.0523,0.222] | -0.0376 | [-0.148,0.0728] | -0.0514 | [-0.183,0.0805] | -0.0930* | [-0.177,-0.00873] | 0.0533* | [0.00606,0.101] |
| 5th | 0.0872 | [-0.00461,0.179] | 0.0295 | [-0.0763,0.135] | 0.0963 | [-0.0411,0.234] | 0.0641 | [-0.0478,0.176] | -0.032 | [-0.163,0.0989] | -0.00487 | [-0.0897,0.0800] | 0.141*** | [0.0928,0.189] |
| Urban- rural indicator | | | | | | | | | | | | | | |
| RU 1 | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] | 0 | [0,0] |
| RU 2 | -0.0266 | [-0.0914,0.0382] | -0.0381 | [-0.111,0.0353] | -0.0801 | [-0.174,0.0140] | -0.0439 | [-0.123,0.0350] | -0.0979* | [-0.190,-0.00537] | -0.0142 | [-0.0734,0.0450] | -0.0261 | [-0.0596,0.00746] |
| RU 3 | -0.0219 | [-0.120,0.0762] | -0.0543 | [-0.171,0.0622] | -0.0129 | [-0.157,0.132] | -0.0917 | [-0.214,0.0304] | -0.174* | [-0.319,-0.0289] | 0.0000123 | [-0.0958,0.0958] | -0.0650* | [-0.118,-0.0119] |
| RU 4 | -0.205* | [-0.376,-0.0337] | -0.154 | [-0.358,0.0499] | -0.129 | [-0.354,0.0960] | -0.295** | [-0.504,-0.0864] | -0.296* | [-0.569,-0.0230] | -0.183* | [-0.339,-0.0281] | -0.0412 | [-0.133,0.0509] |
| RU 5 | -0.113 | [-0.332,0.107] | -0.328* | [-0.643,-0.0123] | -0.0805 | [-0.445,0.284] | -0.156 | [-0.417,0.105] | -0.00105 | [-0.285,0.282] | -0.11 | [-0.340,0.119] | -0.137* | [-0.252,-0.0215] |
| RU 6 | -0.00187 | [-0.114,0.111] | -0.192** | [-0.322,-0.0614] | -0.108 | [-0.262,0.0465] | -0.209** | [-0.338,-0.0615] | -0.168 | [-0.342,0.00572] | -0.0725 | [-0.171,0.0260] | -0.0368 | [-0.0970,0.0234] |
| Constant | 9.557 | [8.553,10.56] | 11.24 | [10.07,12.42] | 9.733 | [8.051,11.42] | 8.481 | [7.260,9.702] | 11.00 | [9.555,12.45] | 9.332 | [8.407,10.26] | 9.660 | [9.153,10.17] |
| Observations | 3185 | | 2262 | | 1117 | | 1792 | | 1276 | | 2621 | | 14133 | |

95% confidence intervals in brackets

* p < 0.05, ** p < 0.01, *** p < 0.001

## 6.C.3. English papers

**Healthcare trajectories and costs in the last year of life: a retrospective primary care and hospital analysis.**

Download using: https://spcare.bmj.com/content/early/2020/12/01/bmjspcare-2020-002630.abstract

**Patterns and costs of hospital-based cancer care in the last year of life: A national data linkage study in England**.

Download using:
https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.e18769

# Appendix - Clinical Trials

## 6.D.1. Appendix - EPAT

Does an institutionalised approach to cancer pain assessment and management result in more individualised and cost efficient care?

**Appendix 1**

EPAT Tools and Algorithms

Appendix 1 EPAT tool combined.pdf

**Appendix 2**

| Costs - Length of Stay (LoS) | | |
|---|---|---|
| Source | Description | Cost/day |
| PSSRU 2018 | Daycase | 745 |
| National schedule of reference costs (2017/18) | Daycase | 742 |
| * Decided for the "Daycase" costs as opposed to inpatient costs as the inpatient cost reflect a spell of care rather than a per diem cost. | | |

| Costs - Interventions | | |
|---|---|---|
| Intervention | Cost/Intervention | Assumption/Description |
| Local Nerve Block | 160 | Nerve Block or Destruction of Nerve, for Pain Management |
| Coeliac plexus block | 160 | Nerve Block or Destruction of Nerve, for Pain Management |
| Cordotomy | 160 | Assumption based on the price for a Local nerve block |
| External epidural | 133 | Epidural Under Image Control for Pain Management |
| External intrathecal | 360 | Assumption based on the price |

| | | |
|---|---|---|
| Implanter intrathecal | 360 | Insertion of Intrathecal Drug Delivery Device for Treatment of Neurological Conditions, 19 years and over |
| TENS | 10 | Assumption (Price of Tens Unit at local Pharmacy £59 99 [25/01/2019]) |
| Acupuncture | 957 | Acupuncture for Pain Management |
| Heat | 5 | Assumption (Price at local Pharmacy [25/01/2019]) |
| Cold | 2.5 | Assumption (Price of Tens Unit at local Pharmacy £24 99 [25/01/2019]) |
| Radiotherapy | 103 | *Deliver a Fraction of Treatment on a Megavoltage Machine £103 |
| All costs are NHS reference costs 2017/18 unless stated otherwise | | |

| Name | Dose | Unit | Cost per pack (BNF) | Cost/Unit | Assumption |
|---|---|---|---|---|---|
| Aspirin | 5 | ml | | 0.04 | |
| Aspirin | 10 | ml | | 0.04 | |
| Aspirin | 75 | mg | 28 tablets 1.12 | 0.04 | |
| Aspirin | 150 | mg | | 0.08 | |
| Aspirin | 300 | mg | 100 tablets 10.78 | 0.1078 | |
| Aspirin | 390 | mg | | 0.2156 | |
| Aspirin | 600 | mg | | 0.2156 | |
| Paracetamol | 1 | g | 100 tablets 2.50 | 0.025 | |
| Paracetamol | 1.5 | g | | 0.0403 | |
| Paracetamol | 2 | g | | 0.05 | |

| | | | | | |
|---|---|---|---|---|---|
| Paracetamol | 2.5 | g | | 0.0653 | |
| Paracetamol | 3 | g | | 0.075 | |
| Paracetamol | 5 | g | | 0.1 | |
| Paracetamol | 500 | mg | 100 tablets 1.53 | 0.0153 | |
| Paracetamol | 1000 | mg | 100 tablets 2.50 | 0.025 | |
| Co-codamol 8/500 | 8/500 | | | 0.024666667 | |
| Co-codamol 8/500 | 1 | tabs | 30 tablets 0.74 | 0.024666667 | |
| Co-codamol 8/500 | 1.5 | tabs | | 0.037 | |
| Co-codamol 8/500 | 2 | tabs | | 0.049333333 | |
| Co-codamol 15/500 | 15/500 | | 100 tablets 3.56 | 0.0356 | |
| Co-codamol 15/500 | 2 | tabs | | 0.0712 | |
| Co-dydramol | 10 | ml | | 0.198928571 | |
| Co-dydramol | 1 | g | 20mg/500mg tablets 56 for 5.57 | 0.198928571 | |
| Co-dydramol | 2 | tabs | | 0.198928571 | |
| Co-codamol 30/500 | 30/500 | | 100 tablets 4.14 | 0.0414 | |
| Co-codamol 30/500 | 30 | mg | | 0.0414 | |
| Co-codamol 30/500 | 500 | mg | | 0.0414 | |
| Co-codamol 30/500 | 1 | tabs | | 0.0414 | |
| Co-codamol 30/500 | 2 | tabs | | 0.0828 | |
| Codeine Phosphate | 1 | g | | 2.438 | |
| Codeine Phosphate | 30 | g | | 2.438 | |
| Codeine Phosphate | 60 | mcg | 60 mg/ml 10 ampoules for 24 38 | 2.438 | |

| | | | | | |
|---|---|---|---|---|---|
| Codeine Phosphate | 15 | mg | 28 tablets for 0.74 | 0.026428571 | |
| Codeine Phosphate | 20 | mg | | 0.031071429 | £ from 30mg |
| Codeine Phosphate | 22.5 | mg | | 0.031071429 | £ from 30mg |
| Codeine Phosphate | 30 | mg | 28 tablets for 0.87 | 0.031071429 | |
| Codeine Phosphate | 45 | mg | | 0.0575 | |
| Codeine Phosphate | 60 | mg | 28 tabs for 1.48 | 0.052857143 | |
| Codeine Phosphate | 90 | mg | | 0.083928571 | |
| Codeine Phosphate | 120 | mg | | 0.105714286 | |
| Co-proxamol | 2 | tabs | 100 tablets 1.53 | 0.0153 | |
| Dihydrocodeine | 2 | tabs | | 0.061428571 | |
| Dihydrocodeine | 30 | mg | 28 tablets 0 86 | 0.030714286 | |
| Dihydrocodeine | 60 | mg | | 0.061428571 | £ from 30mg |
| Tramadol | 5 | mg | | 0.076666667 | £ from 50mg |
| Tramadol | 40 | mg | | 0.076666667 | £ from 50mg |
| Tramadol | 50 | mg | 60 for 4 60 | 0.076666667 | |
| Tramadol | 75 | mg | 60 for 5.15 | 0.085833333 | |
| Tramadol | 100 | mg | 60 for 18 | 0.3 | NHS indicative price |
| Tramadol | 150 | mg | 60 for 23 28 (NHS indicative price) | 0.388 | |
| Tramadol | 200 | mg | 60 for 31.04 (NHS ind. ) | 0.517333333 | |
| Tramadol | 250 | mg | | 0.594 | |
| Tramadol | 500 | mg | | 1.334666667 | |

## 6.D.2. Appendix ENeRgy

This section contains several files.

1. Baseline questionnaire
2. Follow-up questionnaire
3. Published trial protocol as in *Pilot and Feasibility Studies*
4. Published ENeRgy study as in *Journal of Cachexia, Sarcopenia and Muscle*

## 1. Baseline questionnaire ENeRgy

# Baseline Patient Questionnaire

**To be completed at baseline**

**Date of Completion:** _____

**Patient Initials:** _____

**Participant Trial Number:** _____

### Completion Instructions

When you entered the trial you kindly agreed to complete this questionnaire. This is an important part of the trial and we would very much appreciate your efforts in completing and returning it. The research nurse can assist you if required.

The following pages contain questions that relate to you, your present health state and how any intervention is affecting you.

Once you have completed the questionnaire please just hand it to the research nurse.

**Thank you very much for your time and effort.**

# Baseline Patient Questionnaire

## Health questions

EUROQOL© EQ-5D-5L (2015)

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

**SELF-CARE**

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

**PAIN / DISCOMFORT**

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

**ANXIETY / DEPRESSION**

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

# Baseline Patient Questionnaire

We would like to know how good or bad your health is TODAY.

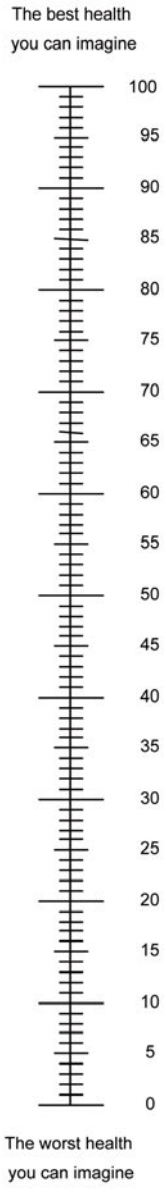
- This scale is numbered from 0 to 100.

  100 means the best health you can imagine.

  **0** means the worst health you can imagine.

- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

**YOUR HEALTH TODAY =** ☐



# Baseline Patient Questionnaire

## Support from family, friends or other carers

When you are answering these questions **for the first time please refer to the last three months**. After that please **refer to the time between** the last questionnaire and the current one.

Have you received help or support from family or friends? Yes ☐ No ☐

- If yes, how much time on average have they spent helping you?

___hours/week

If answered yes to receiving support from family or friends:

- Did they take any time off work to help or support you? Yes ☐ No ☐
- If yes, how much time in total did they take off?

_____days

Are you receiving help, care or support from any other person or organisation (governmental, charities, church)? Yes ☐ No ☐

- If yes please name the organisation(s): _____

- Organisation 1:_____ • _____
- Organisation 2:_____ • _____
- Organisation 3:_____ • ___ hours/week

Do you receive any state benefits (excluding pension) or other financial support? Yes ☐ No ☐

If yes please specify: _____

_____

ENeRgy
Exercise and Nutritional Rehabilitation in patients with advanced cancer

End of questionnaire ***Thank you for your time and effort***

## 2. Follow-up questionnaire ENeRgy

# Follow up Patient Questionnaire

**Date of Completion:** _____

**Patient Initials:** _____

**Participant Trial Number:** _____

**Time-point:** Midpoint Assessment (week 5) ☐

Endpoint Assessment (week 9) ☐

### Completion Instructions

When you entered the trial you kindly agreed to complete this questionnaire. This is an important part of the trial and we would very much appreciate your efforts in completing and returning it. The research nurse can assist you if required.

The following pages contain questions that relate to you, your present health state and how any intervention is affecting you. Please complete them to record the amount of care you have received and expenses you have incurred, including help and support from your family, friends, social welfare benefits and charities.

Once you have completed the questionnaire please just hand it to the research nurse.

**Thank you very much for your time and effort.**

# Follow up Patient Questionnaire

## Health questions

EUROQOL© EQ-5D-5L (2015)

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

**SELF-CARE**

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

**PAIN / DISCOMFORT**

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

**ANXIETY / DEPRESSION**

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

# Follow up Patient Questionnaire

We would like to know how good or bad your health is TODAY.

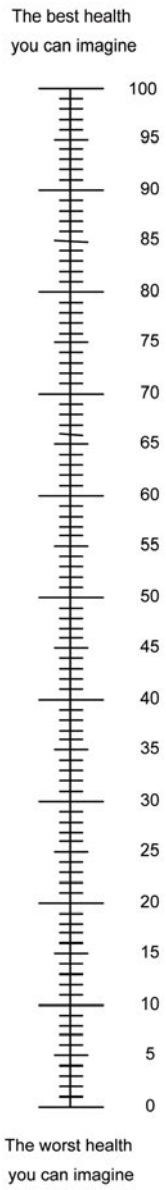
- This scale is numbered from 0 to 100.

  100 means the best health you can imagine.

  **0** means the worst health you can imagine.

- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

**YOUR HEALTH TODAY =** ☐



# Follow up Patient Questionnaire

## Support from family, friends or other carers

When answering this questions please **refer to the time between** the last questionnaire and the current one.

Have you received help or support from family or friends? Yes ☐ No ☐

- If yes, how much time on average have they spent helping you?

___hours/week

If answered yes to receiving support from family or friends:

- Did they take any time off work to help or support you? Yes ☐ No ☐
- If yes, how much time in total did they take off?

_____days

Are you receiving help, care or support from any other person or organisation (governmental, charities, church)? Yes ☐ No ☐

- If yes please name the organisation(s): _____

- Organisation 1:_____ • _____
- Organisation 2:_____ • _____
- Organisation 3:_____ • ___ hours/week

Do you receive any state benefits (excluding pension) or other financial support? Yes ☐ No ☐

If yes please specify: _____

_____

# Follow up Patient Questionnaire

## Healthcare

Please record the **number** of services you have used **since the last questionnaire** including those due to **any** health problems.

**Hospital**

This refers to any contacts you make with the hospital, or hospice. This includes overnight stays in hospital, hospice and telephone calls **to hospital-based health professionals**.

| **Type of service** | Have you used the service since the last time filling in the questionnaire? *(tick if yes)* | Total number of days |
|---|---|---|
| Hospital inpatient stay (>24 hours, or with an overnight stay) | ☐ | _____ |
| • If yes, please specify a reason:_____ | | |
| Unscheduled hospital assessment (<24hrs without an overnight stay) | ☐ | < 1 |
| • If yes, please specify a reason:_____ | | |
| Hospice inpatient stay (>24 hours, or with an overnight stay) | ☐ | _____ |
| • If yes, please specify a reason:_____ | | |
| Have you contacted any health professional based within a hospital (Not including the hospice or your palliative care nurse): such as Hospital doctor, Surgeon, Hospital nurse specialist, Physiotherapist, other<br>• If yes, please specify:<br>Profession:_____<br>Reason:_____<br>Number of Visits:_____<br>Number of contacts by telephone:_____ | | |

**Community**

# Follow up Patient Questionnaire

This refers to all health care and social care that is **not** based in the hospital. This includes your GP, practice or community nurse, dietitian, home help, physiotherapist etc.

| **Type of service** | **Have you used the service since the last time filling in the questionnaire?** *(tick if yes)* | **Total number of visits** | **Total number of home visits** | **Total number of contacts by telephone** |
|---|---|---|---|---|
| GP, surgery | ☐ | | | |
| NHS 24 | ☐ | | | |
| *Out of hours GP* | ☐ | | | |
| Community Palliative Care Nurse | ☐ | | | |
| Nurse, other* | ☐ | | | |
| Psychiatrist or<br>Psychologist or<br>Psychotherapist | ☐<br>☐<br>☐ | | | |
| Physiotherapist* | ☐ | | | |
| Dietitian* | ☐ | | | |
| OT | ☐ | | | |
| Other: | | | | |

***Excluding the research team involved in the ENeRgy trial**

# Follow up Patient Questionnaire

**Charity or organisation** *(e.g. MacMillan, Maggie's, Breast Cancer Care, Church, Citizen's advice, HMRC… others please specify)*

| Type/name of Charity | Reason/Treatment | Number of visits |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

## Travel

This section refers to how much you spent on travel (please do not include the travel expenses connected to the participation in the study) to attend hospital, GP or other health and social care appointments, including any unplanned visits. When you are answering these questions, **please consider the period since last filling in the questionnaire.**

How many miles have you travelled by car? _____ miles

How much have you spent on health-care related parking? £ _____

How much have you spent on fares for public transport, taxis, etc.? £ _____

## Other services and possible expenses

# Follow up Patient Questionnaire

Have you personally incurred any other services and possible expenses due to your health or treatment? (e.g. home adaptations, extra laundry, cleaning services)
Please fill in **all services used, by whom they were provided and in case you had to pay for them, let us know the amount of out of pocket (OOP) expenses.**

| **Description** | **Provided by:** | **If OOP: cost (£)** |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |

ENeRgy
Exercise and Nutritional Rehabilitation in patients with advanced cancer

End of questionnaire ***Thank you for your time and effort***

## 3. Published trial protocol

Hall et al. Pilot and Feasibility Studies (2018) 4:192
https://doi.org/10.1186/s40814-018-0381-6

Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

# A randomised, phase II, unblinded trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) versus standard care in patients with cancer: feasibility trial protocol

Charlie C. Hall[1,2*], Lucy Norris[2], Liz Dixon[3], Jane Cook[1], Matthew Maddocks[4], Catriona Graham[5], Sharon Tuck[5], Erna Haraldsdottir[1], Duncan Brown[1], Anna Lloyd[1], Anne Finucane[6], Peter Hall[7], Katharina Diernberger[7], Richard J. E. Skipworth[8], Marie Fallon[1,2†] and Barry J. Laird[1,2†]

## Background

Patients are living longer with incurable cancer [1] such that in many cases, cancer is likened to a chronic disease [2–4]. This development has wide-ranging implications for both patients and wider society, with increased longevity comes increased morbidity and associated socio-economic burden [5, 6]. Primary cost drivers for patients with advanced cancer are hospitalisation, GP and domiciliary visits [7]. Rehabilitation has been advocated as one such way of optimising the function and quality of life in this group of patients [8]; however, the optimal components of a rehabilitation model for patients with incurable cancer remain to be elucidated.

In the past, there was a therapeutic nihilism that functional decline, cachexia and psychological distress were inevitable consequences of cancer [9, 10]. This is no longer the case and differs markedly from the modern palliative care approach, where advancements in symptom management, embraced in holistic care, have made dramatic improvements in the care of patients over the past 30 years. However, this progress has been slow to incorporate rehabilitation; indeed optimising physical function and nutritional status has largely been ignored [11]. Patients, their families and clinicians realise that optimising quality of life is a fundamental component of good cancer care and that maintaining physical function and nutrition is as important as good symptom control [12]. Although clear guidance exists on symptom control, programmes which optimise physical and nutritional function have been the exception rather than the norm.

The concept of rehabilitation is widely established for the management of chronic diseases such as chronic respiratory disease [13]; yet in palliative care, the concept of rehabilitation remains largely elusive. Rehabilitation in the context of patients with incurable cancer aims to improve function where there is a capacity to do so, to maintain function where the effects of the illness or its treatment threaten to cause decline and to ease the transition toward functional decline where deterioration is inevitable [14].

In 2015, Hospice UK published a report advocating that "rehabilitative palliative care is an essential component of palliative care" [8]. This comprehensive report argued that rehabilitation should focus on function, be person-centred and enable patients to live fully by maintaining or adapting their functional independence while supporting self-management. Guidance was also offered on how rehabilitation should be implemented in the UK, including adopting and embedding a culture of rehabilitative palliative care. However, there is limited robust evidence on which to base this approach. A recent systematic review examining rehabilitation in advanced cancer identified only a small number of studies in this area [4]. Evidence suggests that rehabilitation may be feasible for patients with advanced cancer, but key components are not clear and no firm recommendations could be given. A further review has highlighted the lack of studies examining combined exercise and nutrition interventions for patients with advanced cancer [11].

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Full list of author information is available at the end of the article

While there is evidence of the benefits of rehabilitation in non-malignant conditions, such as chronic respiratory disease [13], extrapolating these models to incurable cancer care needs evaluation. The majority of work to date in patients with incurable cancer has focused on exercise as a single intervention [15]. Although exercise is important, it has been argued that any rehabilitation programme in incurable cancer should also focus on nutritional aspects [11]. This would seem logical as approximately 20% of cancer deaths are directly attributable to cancer cachexia, and cachexia is highly prevalent in patients with advanced cancer [9, 16]. Cachexia is the multifactorial syndrome, defined by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support, causing progressive functional impairment [17]. Optimising nutrition is fundamental to facilitate post-prandial anabolism, which is key to maintaining muscle and thus physical function [18]. There is a persuasive argument that exercise and nutrition should be considered as cornerstones of rehabilitation programmes in patients with incurable cancer [19]. However, this remains to be demonstrated in clinical practice.

Previous studies have demonstrated the detrimental effect of deteriorating physical function on survival [20]. It therefore follows that optimising physical function may have survival benefits. At the very least, it may enable patients to remain independent for longer periods. Previous work by our group has examined an exercise and nutrition-based intervention in oncology outpatients with lung and pancreatic cancer undergoing chemotherapy and demonstrated that such an intervention was feasible and had beneficial effects on physical function and weight [21]. A recent randomised control trial has shown good adherence to an exercise and nutritional intervention in palliative lung and gastrointestinal cancer patients, with beneficial effects on symptoms of nausea and vomiting and protein intake [22].

These findings are encouraging; however, the potential benefits of an exercise and nutrition-based rehabilitation programme in a general population of patients with incurable cancer remain unclear. The ENeRgy trial aims to determine whether an exercise and nutritional rehabilitation programme is feasible in a hospice outpatient setting for patients with incurable cancer. It aims to also examine changes in physical function, nutritional status and quality of life in these patients. Effects on partner-carer quality of life as well as healthcare resource utilisation will also be examined. A companion qualitative study, 'ENeRgy-Q', will be undertaken to explore acceptability, compliance and the psychosocial impact of this rehabilitation programme for patients with incurable cancer in the hospice setting.

## Methods

### Design

This is a randomised, unblinded feasibility trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) versus standard care in patients with incurable cancer. Full ethical approval has been given (17/WS/0226), and the trial will be conducted according to principles of Good Clinical Practice and the Declaration of Helsinki.

### Population

Eligible patients will meet the following key criteria: ≥ 18 years of age, Karnofsky Performance Status (KPS) ≥ 60, diagnosis of incurable cancer (defined as metastatic or locally advanced cancer not amenable to curative treatment), not undergoing anti-cancer therapy (hormonal treatment or bisphosphonates permitted) with a prognosis greater than 3 months. Eligible patients are community-dwelling and have the capacity to consent and complete trial-based assessments. Participants will be identified and referred to the trial from one of two hospice community palliative care teams or from the regional oncology service. Patients undergoing anti-cancer therapy (excluding hormone or bisphosphonate treatments), using enteral nutrition, unable to swallow or co-enrolled in drug trials are excluded. Figure 1 details the trial schematic. The consent process will be opt in, and written informed consent will be obtained by the trial research nurse or doctor. After baseline assessments (which occur over 7 days; week 0), patients will be randomised (1:1 stratified by baseline KPS 60–80%, 90–100%) to receive either an 8-week exercise and nutrition-based rehabilitation programme (treatment arm) or standard care (control arm). Patients randomised to the control arm will be offered the study intervention after trial completion.

The trial is being conducted in a single centre (a hospice) serving a geographically defined region in the UK with a population of approximately one million. Trial-related assessments will take place at an outpatient clinic at this hospice. Management of the trial will be overseen by a Trial Management Group (TMG). Patient and public involvement (PPI) for the trial has been provided by Marie Curie's Expert Voices group, as well as an ex-carer of a patient with cancer. PPI input has been highly valued, ranging from design of trial documents to regular presence at TMG meetings.

### Interventions

#### *Treatment arm*

The treatment arm is an exercise and nutrition-based rehabilitation programme. Patients allocated to this arm will have an interview with the trial physiotherapist and dietitian at week 1. They will then be given an individualised exercise and nutrition-based rehabilitation

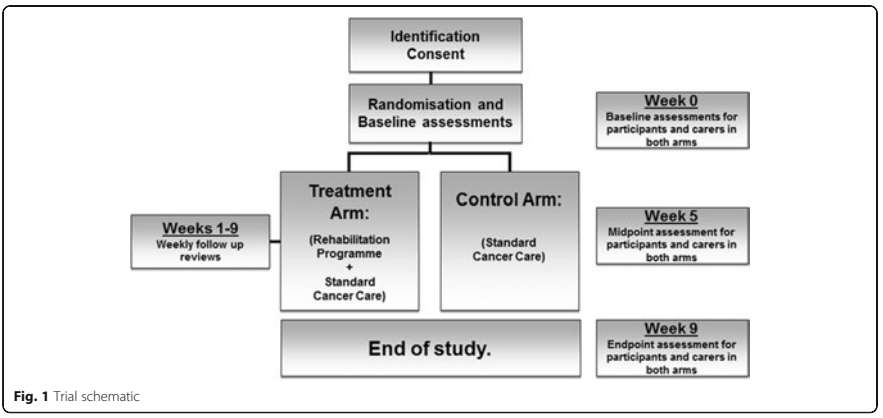


**Fig. 1** Trial schematic

programme following this assessment. Key components of this include the following:

**Exercise** A home-based exercise programme is supported by a booklet. This will consist of aerobic and resistance exercise in divided sessions of the patient's choosing. The aerobic component comprises a total of 60 min of physical activity over the course of each week at moderate intensity, i.e. feeling warm and getting slightly out of breath (able to talk), equivalent to an intensity of 3–4 rating of perceived exertion on a modified Borg scale [23]. Walking will be recommended as the main type of physical activity although cycling or more vocational forms of activity, e.g. heavy housework and gardening, can be used as long as they provoke the desired level of exertion. The resistance component involves major muscle groups in the upper and lower body (e.g. half squats, standing press-ups, shoulder press) and will be recommended three times per week. Patient diaries will record the amount of resistance and aerobic exercise taken daily and any difficulties with particular exercises.

**Nutrition** The main goal of the nutritional intervention is to promote energy balance and to ensure optimal nutritional intake. The nutritional component consists of individual dietary counselling to enhance overall dietary intake [19, 21] and oral nutritional supplements (ONS).

Individual dietary counselling will continue weekly throughout the trial by the trial dietitian. Dietary advice will be tailored and take into account any specific requirements, e.g. ethnic background. Patients will be instructed to take two ONS per day. One ONS portion (220 mL) contains 1 g of eicosapentaenoic acid (EPA), and the caloric distribution is relevant for cancer patients experiencing unintended weight loss. Patients not able to tolerate the ONS due to personal preference will be offered an alternative ONS plus capsules containing 2 g EPA. Patient information leaflets will detail varied ways to take the ONS to improve compliance, and diaries will record the numbers of ONS taken daily.

At weekly review appointments, patient diaries will be reviewed by the research nurse for healthcare-related resource use; adverse events will also be screened for and logged. The trial dietitian will review the patients' dietary intake and compliance with the ONS, and the trial physiotherapist will review exercise progress, offer goal setting and prompt any changes needed to maintain compliance.

### *Control arm*

Patients randomised to the control arm will continue to receive standard care from their GP and community palliative care team on an as required basis according to individual patient need. This care may also include referral to other members of the community-allied healthcare professional MDT team if required (for example counsellors, occupational therapist or social workers). The control group will be phoned at weekly intervals by the research nurse to ascertain levels of healthcare-related utility and adverse events. In the control group, patients will also have diaries to record any (non-trial) nutritional supplements they are taking as well as the amount and type of exercise undertaken each week. This will help gauge any degree of contamination in the control group.

Patients in the control arm will be offered the opportunity to undertake the rehabilitation programme at the end of their involvement in the trial if they wish to do so.

### Outcomes

The primary endpoint is to evaluate the feasibility of delivering the exercise and nutritional rehabilitation programme in a hospice outpatient context. This will be assessed by measuring compliance with the rehabilitation programme (numbers of exercises and nutritional supplements versus those advised). Compliance with trial procedures will also be measured, including completion of diaries and questionnaires, percentage withdrawal, completion of physical tests and completeness of physical activity monitor data.

Secondary endpoints will examine the feasibility of recruitment and retention, evidence of contamination in the control group and change in physical function and nutritional status. Quality of life measures for patients (± partner-carers) and impact on patient healthcare-related resource use in terms of cost between sectors of the NHS, social services, third sector, participant expenses and carer costs will also be examined. All endpoints will be assessed at baseline (pre-randomisation—week 0) and at trial endpoint (week 9). Table 1 details a summary of trial-related assessments and time points.

### Statistical considerations

The primary endpoint of this study is to assess the feasibility of the treatment (an exercise and nutrition-based rehabilitation programme). As such, a formal sample size calculation has not been performed. We plan to recruit over a 13-month period and expect to be able to obtain at least 40 participants over that timeframe. Intention-to-treat analysis will be performed.

The primary outcome measures will be presented descriptively using appropriate summary statistics with corresponding 95% confidence intervals. Demographic statistics and exploratory outcome measures shall also be presented using appropriate summary split by treatment group. Continuous outcome measures, for example, change in daily step count and change in weight, will be compared between treatment arms using two sample $t$ tests or non-parametric equivalent as appropriate. Rates of compliance will be reported along with completion rates for all other outcome measures. This feasibility trial is not powered to explore efficacy, but these estimates of variability will be used to inform the sample size and inform our choice of primary endpoint for the definitive trial. There are no plans to perform an interim analysis while recruitment is ongoing or before follow-up is completed. Estimation of economic parameters will rely on questionnaires designed to measure health-related utility, healthcare-related resource use and costs, administered at baseline and follow-up assessment time points. Unit costs will be assigned using standard national costing sources where available or through consultation with relevant service business managers. Costs

**Table 1** Trial related assessments and time points (both arms)

| | Baseline measures (week 0) | Midpoint (week 5) | Endpoint (week 9) |
|---|---|---|---|
| Demographics | • Gender, primary tumour site and tumour status; metastatic sites; current hormone/bisphosphonate or steroid treatment | • N/A | • N/A |
| Physical measures | • Height<br>• Weight | • Weight | • Weight |
| Quality of life (QOL) measures | • Patient QOL (EORTC QLQ-C15-PAL questionnaire) [24]<br>• Partner-Carer QOL[a] (Caregiver Quality of Life Index-Cancer Questionnaire (CQOLC)) [25]<br>• EQ-5D-5L & EQ-VAS [26] questionnaires | • Patient QOL (EORTC QLQ-C15-PAL)<br>• Partner-Carer QOL[a] (CQOLC)<br>• EQ-5D-5L & EQ-VAS questionnaires | • Patient QOL (EORTC QLQ-C15-PAL)<br>• Partner-Carer QOL[a] (CQOLC)<br>• EQ-5D-5L & EQ-VAS questionnaires |
| Functional measures | • Karnofsky Performance Status (KPS) [27]<br>• Life Space Assessment questionnaire (LSA) [28]<br>• Two-minute walk test [29]<br>• Timed up and go test [30] | • KPS<br>• LSA<br>• Two-minute walk test<br>• Timed up and go test | • KPS<br>• LSA<br>• Two-minute walk test<br>• Timed up and go test |
| Socio-economic measures | • Socio-economic background (employment status, benefits received, carer responsibilities, current use of social services)<br>• Healthcare utilisation and expenses questionnaire | • Healthcare utilisation and expenses questionnaire | • Healthcare utilisation and expenses questionnaire |
| Physical activity meter (PAM) | • PAM worn continuously for 7 days[b] (data retrieved at week 1)<br>• Mean daily step count<br>• Hours asleep/ restless/ awake per night | (PAM worn only at baseline and end point) | • PAM worn continuously for 7 days[b] (data retrieved at week 10)<br>• Mean daily step count<br>• Hours asleep/restless/awake per night |
| Nutritional measures | • Abridged Patient-Generated Subjective Global Assessment (aPG-SGA) [31]<br>• Ten-point verbal analogue scale (AveS) [32] | • aPG-SGA<br>• AveS | • aPG-SGA<br>• AveS |

[a]'Partner carer' is a partner with whom the patient is married, cohabiting or non cohabiting, and the patient also describes as their carer
[b]PAM data for weekend days may be excluded to reduce potential variation

will be summarised from the perspectives of (a) the NHS, (b) the charitable and 3rd sector, (c) the patient and their carers and (d) wider society. A proof-of-concept health economic model will be constructed taking the form of a probabilistic decision model that simulates the passage of patients through the clinical pathway defined by discrete health states, allowing estimation of costs, quality of life and survival. The model will be parameterised using data from the feasibility trial where possible, supplemented by data from the published literature. Cost-effectiveness will be presented as the incremental cost-effectiveness ratio (ICER), expressed as cost per QALY gained.

A computer-generated randomisation schedule will be produced using a random block size to allocate patients at random in a 1:1 ratio to either the treatment arm (personalised exercise and nutrition-based rehabilitation programme) or control arm (standard care) via sealed envelopes. The randomisation will be stratified by performance status due to its influence on prognosis to ensure that patients with differing prognoses are equally distributed between arms (KPS of 60–80% versus KPS 90–100%). Randomisation will occur at baseline (week 0) but will be blinded to patients until week 1 when it will be revealed by the research nurse so as not to influence baseline activity levels in either group during baseline assessments.

Paper case report forms (pCRF) will be used, and data will be entered directly into an electronic data base. A 10% check will be undertaken on all inputted data to ensure validity. Patients will be identified by a unique trial identification number, and patient identifiable data will be kept locked securely within the hospice. Standard operating procedures (SOPs) issued by the trial sponsor (ACCORD/NHS Lothian) will be adhered to for example reporting deviations from the protocol or serious adverse events (SAEs).

## Discussion

One of the fundamental arguments supporting rehabilitation is the changing face of cancer. Although initially regarded as a terminal disease, cancer is morphing into a chronic condition which in combination with its increasing incidence will mean that more patients are 'living with' rather than 'dying from' their cancer. Combined with an ageing population, this means that the population who would fit under the umbrella of palliative care is likely to rise considerably over the coming decades. It is important that in view of this potential increase in patient numbers, the overall condition of patients is optimised through maximisation of physical function and nutritional status.

The ENeRgy trial is a key step in defining, developing and assessing the feasibility of an exercise and nutrition-based rehabilitation programme in this patient cohort. We will use the trial to test the mechanism of healthcare resource use data capture with a view to identifying key possible drivers of cost differences. The results of this trial and subsequent studies have the potential to significantly impact and influence the approach to rehabilitation for patients with incurable cancer in the future.

## Trial status

The description of the trial is in keeping with the approved version of the trial protocol (version 3, date 15 April 2018). The trial has been open to recruitment from 30 January 2018, and recruitment is expected to last 13 months, ending on 28 February 2019.

### Abbreviations

aPG-SGA Abridged Patient Generated Subjective Global Assessment; AveS Ten-point verbal analogue scale for dietary intake; CQOLC Caregiver Quality of Life Index- Cancer Questionnaire; ENeRgy Exercise and Nutrition-based Rehabilitation programme (ENeRgy); EORTC QLQ-C15-PAL A questionnaire developed to assess the quality of life of palliative cancer care patients; EPA Eicosapentaenoic acid; EQ-5D-5L & EQ-VAS Euroqol questionnaires regarding quality of life The 5D is five level descriptive questionnaire and the VAS is a visual analogue scale; GP General practitioner; KPS Karnofsky Performance Status; LSA Life Space Assessment questionnaire; ONS Oral nutritional supplement; PAM Physical Activity Monitor; pCRF Paper case report form; QOL Quality of Life; SAEs Serious adverse events; SOPs Standard operating procedures

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### Availability of data and materials

Not applicable

### Trial sponsor

ACCORD/NHS Lothian Contact Chris Coner Chris Coner@ed ac uk

**Authors' contributions**
CH, BL, MF, LN, LD, JC, MM, CG, ST, PH and KD contributed to the writing of the trial protocol and this manuscript In particular, MM assisted with the design and of the exercise programme PH and KD helped design and refine the health-economic components CG and ST contributed in the statistical analysis sections AF, AL, EH, DB and RS have had roles from developing the trial funding proposal to forming the trial management group which has influenced the protocol and this manuscript All authors read and approved the final manuscript

**Ethics approval and consent to participate**
The West of Scotland Research and Ethics Committee board 4 have approved this trial (Reference 18/WS/0226) Informed consent will be obtained from all participants upon enrolment into the trial

**Consent for publication**
Not applicable

**Competing interests**
The authors declare that they have no competing interests

## Publisher's Note



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## 4. ENeRgy published paper

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# A randomized, feasibility trial of an exercise and nutrition-based rehabilitation programme (ENeRgy) in people with cancer

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## Abstract

**Background** Despite rehabilitation being increasingly advocated for people living with incurable cancer, there is limited evidence supporting efficacy or component parts. The progressive decline in function and nutritional in this population would support an approach that targets these factors. This trial aimed to assess the feasibility of an exercise and nutrition based rehabilitation programme in people with incurable cancer.

**Methods** We randomized community dwelling adults with incurable cancer to either a personalized exercise and nutrition based programme (experimental arm) or standard care (control arm) for 8 weeks. Endpoints included feasibility, quality of life, physical activity (step count), and body weight. Qualitative and health economic analyses were also included.

**Results** Forty-five patients were recruited (23 experimental arm, 22 control arm). There were 26 men (58%), and the median age was 78 years (IQR 69–84). At baseline, the median BMI was 26 kg/m$^2$ (IQR: 22–29), and median weight loss in the previous 6 months was 5% (IQR: −12% to 0%). Adherence to the experimental arm was >80% in 16/21 (76%) patients. There was no statistically significant difference in the following between trial arms: step count − median % change from baseline to endpoint, per trial arm (experimental −18.5% [IQR: −61 to 65], control 5% [IQR: −32 to 50], $P = 0.548$); weight − median % change from baseline to endpoint, per trial arm (experimental 1%[IQR: −3 to 3], control −0.5% [IQR: −3 to 1], $P = 0.184$); overall quality of life − median % change from baseline to endpoint, per trial arm (experimental 0% [IQR: −20 to 19], control 0% [IQR: −23 to 33], $P = 0.846$). Qualitative findings observed themes of capability, opportunity, and motivation amongst patients in the experimental arm. The mean incremental cost of the experimental arm versus control was £-319.51 [CI −7593.53 to 6581.91], suggesting the experimental arm was less costly.

**Conclusions** An exercise and nutritional rehabilitation intervention is feasible and has potential benefits for people with incurable cancer. A larger trial is now warranted to test the efficacy of this approach.

**Keywords** Exercise; Nutrition; Cancer; Rehabilitation

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## Introduction

Cancer is becoming more common, yet advances in treatment mean that more people are living longer with incurable disease than ever before.[1] Indeed the number of people living with cancer is increasing by approximately 3% every year with life expectancies of several months to years.[2] Further, with population aging, people with incurable cancer are increasingly older, living longer, and have more co-morbidities.

Langbaum and Smith argue that 'many people with cancer function fully for years, and it is commonplace for patients with chronic cancer to face the challenge of determining how to optimize their remaining time'.[1] This view is being increasingly acknowledged by learned societies with the European Society of Medical Oncology (ESMO)[3] and American Society of Clinical Oncology (ASCO),[4] supporting rehabilitation as a key component of cancer care. Optimizing overall function has been purported to improve quality of life, tolerability of cancer therapies and reduce patient and caregiver distress. Furthermore, this may have positive benefits on health care resource allocation and use. Although these are laudable achievements there remains a paucity of evidence to directly support the benefits of rehabilitation in patients with incurable cancer and to guide the constituent parts of programmes.

It would seem logical that targeting physical and nutritional deficits should be the cornerstones of any rehabilitation intervention. Together, deterioration in physical function combined with loss of muscle and fat termed 'cancer cachexia', result in approximately 50% of cancer deaths, and becomes more prevalent as disease progresses. It has been advocated that to optimally address cachexia, any interventions should be multimodal and comprise nutritional support and exercise advice.[5 8] However, to date, there is limited evidence to support this.

Therefore, a trial was undertaken to assess the feasibility of an exercise and nutritional rehabilitation programme in people with incurable cancer. Termed the ENeRgy trial, this was a randomized, feasibility trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) versus standard care in people with cancer.

## Methods

### *Study design and patients*

We undertook a randomized, open label, feasibility trial at a specialist palliative care unit in the UK, serving a geographically defined population of approximately one million. Eligible patients met the following criteria: outpatients; age ≥18 years; Karnofsky performance status (KPS) ≥ 60; diagnosis of incurable cancer (defined as metastatic or locally advanced cancer not amenable to curative treatment); not undergoing anti-cancer therapy (hormonal treatment and/or bisphosphonates were permitted); a clinician predicted survival of >3 months.

Patients undergoing anti-cancer therapy (hormonal, bisphosphonates permitted), receiving parenteral nutritional support, who had dysphagia or who were co-enrolled in a clinical trial were excluded. Those who had received any systemic anti-cancer therapy in the preceding 4 weeks were not eligible.

The trial was conducted as per Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by an ethics committee for human research (ethics reference: 17/WS/0226). All patients provided written informed consent. The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.[9] The trial was registered at ClinicalTrials.gov: NCT03316157. The rationale and trial design have been previously described.[10]

### *Randomization*

Patients were randomized centrally in a 1:1 ratio of experimental to control, using a block randomization with random block sizes and stratified for baseline KPS (60 80% or 90 100%).

### *Procedures*

The experimental arm was an exercise and nutrition-based rehabilitation programme. Following baseline assessments and randomization, patients had an interview with the trial physiotherapist and dietitian. Based on this interview, they were given personalized advice on nutrition and exercise.

The exercise component, developed by the physiotherapist, was a home-based programme consisting of aerobic and resistance training in divided intervals as per patient choice and capability. The aerobic component totalled 60 min of exercise per week (e.g. walking) at moderate intensity (warm and slightly out of breath modified Borg scale 3 4 rating). The resistance component focussed on major muscle groups in the upper and lower body, predominantly using body weight exercises including standing press ups, half squats and shoulder thrusts, with sets advised three times per week.

The nutrition component aimed to ensure optimal nutritional intake and consisted of dietitian-led counselling (personalized for each patient) taking into account dietary preferences. Patients were also supplied with an Oral Nutritional Supplement (ONS ProSure® Abbott Laboratories, ILL, USA) and advised to take two per day. Each 220 mL supplement contained 1 g of eicosapentaenoic acid (EPA) and

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1.5 kcal/mL. Patients who did not tolerate the ONS due to preference were offered an alternative ONS and oral capsules containing 2 g EPA.

Written information supporting the exercise and nutrition interventions were provided (Supporting Information, *Data* S3). The dietitian and physiotherapist reviewed adherence to the relevant interventions during weekly clinic attendances by patients. At this time, progress was reviewed and the intervention modified if needed, to support adherence. A patient diary (paper) was used to record the number of minutes of aerobic exercise per day, the number of strength exercises performed per day, and the number of nutritional supplements taken per day, and this was discussed with the patient at their weekly visits.

Patients randomized to the control arm received their usual care which may have included ongoing specialist palliative care follow-up as per individual patient need. They were entitled to any additional support from allied health professionals if needed. Those in the control arm received weekly telephone calls from the research team to ensure adherence to trial-related data collection and record any nutritional interventions (dietitian and/or prescribed ONS) and exercise undertaken. These data were collected to assess any contamination of the control group (mimicking any aspect of the trial-related intervention). Patients in the control arm were offered the trial intervention at the end of their involvement in the trial.

### *Endpoints*

The primary endpoint of the trial was to assess feasibility of the experimental arm (rehabilitation programme). Feasibility was assessed primarily by adherence to the intervention using the prescribed number of exercises/ONS prescribed versus actual undertaken. We recorded adherence by using the prescribed versus actual amounts of exercise and nutritional supplements performed/taken. These data were obtained from patient recorded diaries (of which completion was supported by weekly telephone calls by research staff).

Secondary endpoints assessed other aspects of feasibility using recruitment rate (could we recruit our target sample within an acceptable time frame [18 months]), attrition rate (compared with similar studies in patients with advanced cancer), and contamination of the control arm (use of ONS outside the trial and exercise uptake). The acceptable attrition rate was defined as $<44\%$, and this was informed by previous work in palliative and supportive care trials.[11]

The exploratory endpoints examined the following.

Physical function was assessed using a physical activity monitor (Fitbit®, San Francisco, USA). Patients wore this pre-randomization for 7 days then at the end of the trial for 7 days. We assessed mean daily step count at these time points. We also assessed physical function assessed using the timed up and go (TUG) test,[12] 2 min walk test (TMWT),[13] and the Life Space Assessment (LSA) questionnaire.[14] All of these were carried out at baseline (pre-randomization) and at the trial endpoint.

Performance status was assessed at baseline using Karnofsky performance status criteria.[15] Nutritional status was assessed using the abridged Patient Generated Subjective Global Assessment (abPG-SGA),[16] body weight, and assessment of nutritional intake using a 10-point scale (AveS).[17]

Quality of life was assessed using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C15PAL (EORTC QLQ-C15PAL),[18] the EQ-5DL, and the EQ-VAS questionnaires.[19]

Quality of sleep was assessed using sleep data recorded by the physical activity monitor. Adverse events were also assessed and reported.

Health economic endpoints examined the potential impact on patient-reported health utility, healthcare-related resource use and costs. Health utility was assessed by the EQ-5D-5L[20] and EQ-VAS patient completed questionnaire, healthcare utilization, and out of pocket expenses.[19] Questionnaires were designed to measure health-related utility healthcare-related resource use and costs, administered at baseline and follow-up assessment time-points. Patient health-related quality of life was captured using a patient reported outcome measure; the EQ-5D-5L and EQ-VAS questionnaires. Utility values were assigned to responses using the standard UK value set.[21] Healthcare utilization and costs were collected using a bespoke patient completed questionnaire, adapted from the UK Cancer Costs Questionnaire [citation: https://blogs.ed.ac.uk/ukcc/].

Unit costs were assigned to resource use items using standard national costing sources such as PSSRU[22] and NHS reference costs,[23] or through consultation with relevant service business managers. Costs were summarized from the perspectives of the NHS, the charitable and 3rd sector and the patient and their carers. Cost-effectiveness was calculated as the Incremental Cost-effectiveness Ratio (ICER), expressed as cost per QALY gained.

A within-trial cost effectiveness analysis was performed in accordance with the methodological specification of the NICE Guide to the Methods for Health Technology Assessment.[24] Uncertainty was evaluated using probabilistic sensitivity analysis (PSA) and value of information (VoI) analysis, implemented using the bootstrap method (1000 replications). For the PSA and for the VoI Analysis, the SAVI Tool from the University of Sheffield was used.[25]

### *Statistical considerations*

As the primary endpoint of this study was to assess the feasibility of the trial, rather than superiority of the experimental arm over the control arm, a formal sample size calculation

was not necessary.[26] Our justification for the sample size of 40 patients was supported by our previous work,[6] our potential pool of eligible patients (estimated at 1300 per year), consensus in the sample size of feasibility trials,[27] and based on this, we estimated we would be able to express the percentage completing the study protocol to within ±9% assuming a two-sided 95% confidence interval (CI) around an expected percentage of 90% completion. Findings are presented descriptively split by trial arm and endpoints (e.g. change in daily step count and change in weight) are compared between trial arms using appropriate non-parametric tests (Mann Whitney *U* test). No interim analysis was planned or undertaken. The analysis was performed using data from on all patients recruited. SPSS v23 (Chicago, IL, USA) was used.

### *Embedded qualitative study*

Interviews with a purposive sample of experimental arm patients were audio-recorded and transcribed verbatim. Coding of all transcribed data, conducted by two researchers blind to the trial results (A. L. and J. H.), was inductive and focused on the questions: 'What is the experience of ENeRgy?' and 'What are the barriers to and facilitators of the physical activity and nutritional components of ENeRgy?'

The analysis used the framework technique,[28] which involves systematic and interconnected stages of sifting and charting coded qualitative data, then mapping patterns in a search for understanding and explanation. The pre-existing

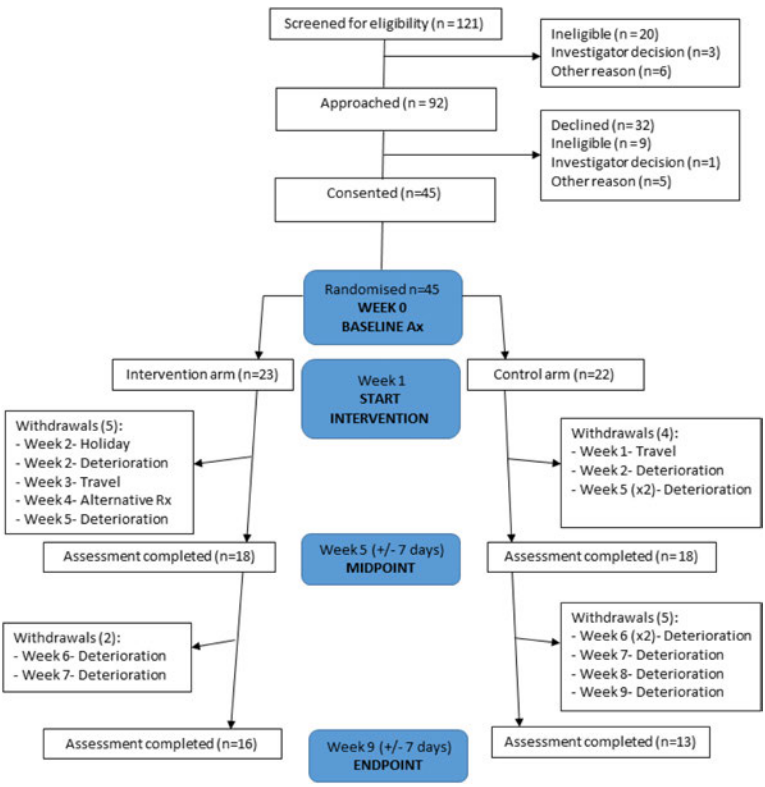


**Figure 1** Trial profile.

framework, Capability, Opportunity, and Motivation together result in Behaviour (COM-B) was applied to the coded data. Coded data extracts were categorized (J. H.) as capability, opportunity, or motivation for physical activity or for nutritional intake. Data relevant to understanding the experience of and engagement with ENeRgy but falling outside the COM-B framework were also captured in a visual representation of the whole data set. Overarching patterns were identified that revealed factors influencing adherence/non-adherence to ENeRgy.

The trial was sponsored jointly by the University of Edinburgh and NHS Lothian.

### *Role of the funding source*

This trial was funded by a grant from Marie Curie and the Chief Scientist Office (Scotland, UK). The oral nutritional supplement was provided free of charge by Abbott Laboratories. The funders and Abbott Laboratories had no involvement in the design, conduct or analysis of the trial. B. L., C. H., M. F., P. H., K. D., E. W., A. L., J. H., and C. G. had access to raw data. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

## Results

From 30 January 2018 to 24 April 2019 (15 months), 45 patients were recruited (23 experimental arm, 22 control arm) (*Figure* 1). Baseline characteristics are shown in *Table* 1. The median age was 78 years (IQR: 69 84) and 26 (58%) were male. The most common primary cancer site was gastrointestinal (18 [40%]), and patients had either metastatic (29 [64%]) or loco-regionally advanced disease (16 [36%]). Twenty-nine (65%) of patients had a Karnofsky performance score of 60 80. The median BMI at baseline was 26 kg/m$^2$ (IQR: 22 29), and the median weight loss in the previous 6 months was 5% (IQR: 12% 0%) (*Figure* 2).

*Table* 2 details the primary endpoints of feasibility of the experimental arm (rehabilitation programme) assessed by adherence to the prescribed exercises/ONS versus actual undertaken. For the experimental arm, adherence was defined as excellent if this was ≥80%, good if this was 50 79% and poor if this was below 50%. For individual components of the experimental arm, excellent adherence was achieved by at least 16/21 (76%) of patients, and for adherence to all components, this was either good (8 [38%]) or excellent (12 [57%]) patients. Therefore, feasibility in terms of compliance to the experimental interventions was acceptable, and the trial was positive in this regard.

Secondary endpoints assessed other aspects of feasibility. The recruitment target was 40 patients over 18 months; however, accrual was better than expected, and 45 patients were recruited over 15 months, and then, recruitment was stopped. Of the 121 people screened, 29 were not eligible and were not assessed further. Of the remaining 92 who were further assessed for participation, 45 (49%) were recruited, 9 (10%) were ineligible, 32 (35%) declined, 1 (1%) was not recruited due to an investigator decision, and 5 (5%) for other reasons. The recruitment rate was 37% (45/121) which was similar to other trials in this patient population.[29,30] The main reason for patients not participating was that they declined (32 [35%]).

Of the 45 patients recruited, 29 (64%) completed the trial resulting in an attrition rate of 36% (16/45). The attrition rate was 30% (7/23) and 41% (9/22) in the experimental and control arms respectively. The most common reason for attrition was deteriorating health (four patients experimental; seven patients control arm).

Contamination in the control arm was low; one patient in the control arm started an ONS and another increased their pre-trial ONS use. Patients in the control arm did not have

**Table 1** Patient characteristics

| | Experimental arm (*n* 23) | | Control arm (*n* 22) | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Age <55 | 6 | 26 | 2 | 9 |
| /55–65/ | /3 | /13/ | /4 | /18/ |
| >65 | /14 | 61 | /16 | 73 |
| Male gender | 14 | 61 | 12 | 55 |
| **Primary cancer** | | | | |
| Gastrointestinal | 12 | 52 | 6 | 27 |
| Thoracic | 1 | 4 | 2 | 9 |
| Breast | 2 | 9 | 4 | 18 |
| Urological/Gyn | 4 | 17 | 6 | 27 |
| Myeloma | 2 | 9 | 3 | 14 |
| Head and neck | 1 | 4 | 0 | 0 |
| Other: (Endocrine) | 1 | 4 | 1 | 5 |
| **Cancer stage** | | | | |
| Loco-regionally | 8 | 35 | 8 | 36 |
| Metastatic | 15 | 65 | 14 | 64 |
| **Current cancer treatment** | | | | |
| Hormonal | 5 | 22 | 7 | 32 |
| Bisphosphonate | 2 | 9 | 2 | 9 |
| Steroids | 6 | 26 | 7 | 32 |
| **Performance status** | | | | |
| 60–80% | 15 | 65 | 14 | 64 |
| 90–100% | 8 | 35 | 8 | 36 |
| **Body mass index** | | | | |
| <18.5 | 4 | 17 | 2 | 9 |
| 18.5–25 | 9 | 39 | 6 | 27 |
| 25.1–30 | 7 | 30 | 9 | 41 |
| >30.1 | 3 | 13 | 5 | 23 |
| **Weight change at baseline(<1 month)** | | | | |
| Weight gained | 4 | 17 | 3 | 14 |
| Loss 0–5% | 18 | 78 | 14 | 64 |
| Loss >5% | 0 | 0 | 5 | 23 |
| Unknown | 1 | 4 | 0 | 0 |
| **Weight change at baseline (<6 months)** | | | | |
| Weight gained | 2 | 9 | 2 | 9 |
| Loss 0–5% | 10 | 43 | 5 | 23 |
| Loss >5% | 7 | 30 | 9 | 41 |
| Unknown | 4 | 17 | 6 | 27 |

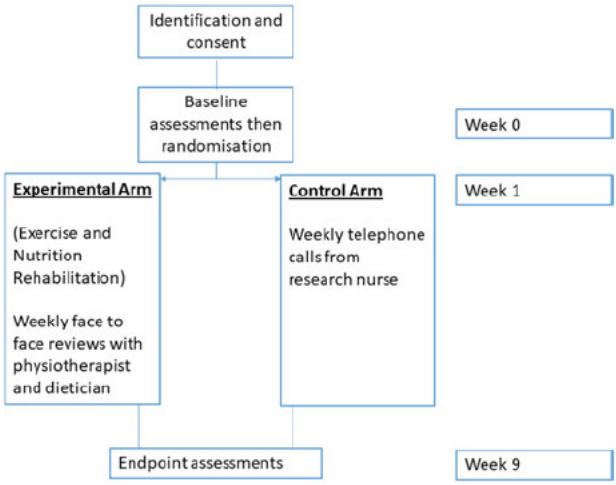


**Figure 2** Trial schematic.

**Table 2** Primary endpoint: adherence to the experimental arm

| Adherence to individual intervention components ($n$ 21)[a] | | | <50% | | ≥50–79% | | ≥80% | |
|---|---|---|---|---|---|---|---|---|
| | | | $n$ | (%) | $n$ | (%) | $n$ | (%) |
| Oral nutritional supplement ($n$ 21) | | | 1 | (5) | 4 | (19) | 16 | (76) |
| Resistance ($n$ 21) | | | 1 | (5) | 3 | (14) | 17 | (81) |
| Aerobic ($n$ 21) | | | 1 | (5) | 2 | (10) | 18 | (86) |
| Adherence to combined intervention components | | | <50% | | ≥50% | | ≥80% | |
| Aerobic | Resistance | | 1 | (5) | 4 | (19) | 16 | (76) |
| Aerobic | ONS | | 1 | (5) | 6 | (29) | 14 | (67) |
| Resistance | ONS | | 1 | (5) | 7 | (33) | 13 | (62) |
| Aerobic | Resistance | ONS | 1 | (5) | 8 | (38) | 12 | (57) |

[a]Two patients withdrew from the trial post randomization.

increased exercise based on self-reported measures and activity data.

*Table* 3 details the exploratory endpoints examining physical function, weight, and nutrition, assessed as part of the trial. There was no evidence of statistically significant differences in the % difference in daily step count ($P$ = 0.548), timed up and go test ($P$ = 0.767), 2-min walk test ($P$ = 0.484), and life space assessment ($P$ = 1.00) between the trial arms. Patients in the experimental arm gained a median of 1% (IQR: −3% to 3%) of weight versus those in the control arm who lost a median of 0.48% (IQR: −2.6% to 0.64%), $P$ = 0.184.

*Table* 4 details the exploratory endpoints examining patient reported outcomes of quality of life measured using the EORTC QLQ-C15 PAL. With the exception of emotional functioning ($P$ = 0.006), there were no statistically significant differences between the trial arms. There was no difference in carer-related quality of life ($P$ = 0.5) or any sleep parameters between the trial arms data not presented).

*Table* 5 details adverse events. There were no SAEs for patients in the trial. There were 39 AEs recorded in total, 20 in the experimental arm (51%), and 19 in the control arm (49%). Of AEs in the experimental arm, nine (45%) were related to the ONS, nine (45%) related to the underlying cancer diagnosis, and two (10%) were due to non-cancer-related issues.

**Table 3** Exploratory endpoints examining physical function, weight, and nutrition

| | | Experimental arm | | Control arm | | |
|---|---|---|---|---|---|---|
| | | *N* | Median (IQR) | *n* | Median (IQR) | *P* |
| Daily step count[a] | Baseline | 22 | 2954 (2168–4143) | 22 | 2294 (591–3821) | |
| | Endpoint | 16 | 2898 (1055–5005) | 12 | 2478 (727–3645) | |
| | Difference | 15 | −476 (−1592–1882) | 12 | 6 (−860–335) | |
| | Difference % | 15 | −19 (−61 to 65) | 12 | 5 (−32 to 50) | 0.548* |
| Timed up-and go test (s) | Baseline | 23 | 13 (11–17) | 22 | 16 (11–24) | |
| | Midpoint | 17 | 15 (12–18) | 15 | 14 (11–27) | |
| | Endpoint | 16 | 14 (12–21.8) | 12 | 15 (12–23) | |
| | Difference | 16 | −0.5 (−3–4) | 12 | 0.5 (−1–2) | |
| | Difference % | 16 | −5 (−18–20) | 12 | 4.5 (−3–12) | 0.767* |
| 2 min walk test (m) | Baseline | 23 | 114 (76–144) | 21 | 104 (66–122) | |
| | Midpoint | 17 | 115 (77–136) | 13 | 107 (52–137) | |
| | Endpoint | 16 | 116 (75–138) | 10 | 106 (68–122) | |
| | Difference | 16 | 9 (−5–18) | 10 | 2 (−10–12) | |
| | Difference % | 16 | 6 (−4–27) | 10 | 2 (−10–15) | 0.484* |
| Life space assessment (max score 120) | Baseline | 21 | 53 (32–81) | 22 | 37(31–52) | |
| | Midpoint | 18 | 38 (34–60) | 16 | 52 (32–66) | |
| | Endpoint | 16 | 50 (35–64) | 13 | 48 (34–58) | |
| | Difference | 16 | 0 (−16–11) | 13 | −2 (−10–5) | |
| | Difference % | 16 | 0 (−21–41) | 13 | −5 (−19–17) | 1.00* |
| Weight | Baseline | 23 | 71 (60–79) | 22 | 70.8 (62–86) | |
| | Midpoint | 17 | 76 (63–85) | 15 | 68 (61–89) | |
| | Endpoint | 16 | 80 (62–88) | 13 | 67(57–87) | |
| | Difference | 16 | 1 (−2–2) | 13 | −3 (−2–0) | |
| | Difference % | 16 | 1 (−3–3) | 13 | −0.5 (−3–1) | 0.184* |
| aPG-SGA score (0–36) | Baseline | 23 | 4 (1–9) | 22 | 6 (2–11) | |
| | Midpoint | 18 | 5 (1–16) | 15 | 6 (1–14) | |
| | Endpoint | 16 | 8 (1–13) | 13 | 6 (1–10) | |
| | Difference | 16 | 1 (−2–5) | 13 | 1 (−3–3) | |
| | Difference % | 16 | 27 (−18–300) | 13 | −42 (−73–117) | 0.249* |
| AveS score (0–10) | Baseline | 23 | 8 (5–8) | 22 | 7 (5–8) | |
| | Midpoint | 18 | 7 (5–9) | 16 | 8 (6–10) | |
| | Endpoint | 16 | 7 (4–10) | 13 | 8 (7–10) | |
| | Difference | 16 | 0 (−1–1) | 13 | 0 (−2–2) | |
| | Difference % | 16 | 0 (−25–22) | 13 | 0 (−16–31) | 0.398* |

*Mann–Whitney *U*-test.
[a]Full 24 h periods.

In the control arm, there were 12 cancer-related AEs (63%) and seven unrelated AEs (37%), relating to pre-existing medical conditions or not serious enough to constitute an SAE.

## Health economic results

Supporting Information, *Data* S1 contains the full health economic analysis results. In summary, the main drivers of costs were hospital inpatient stays and unscheduled hospice stays followed by community care, outpatient appointments, out of hours (OOH) services, and travel costs. The mean incremental cost of the experimental arm versus control is £-319.51 [CI −7593.53 to 6581.91], suggesting the experimental arm is less costly. The mean incremental benefit of the experimental arm versus control was 0.00018 QALYs [CI −0.021, 0.023]. Probabilities of the intervention being cost saving and more beneficial compared with the control group were 0.544 and 0.517, respectively.

## Qualitative analysis

Fourteen patients in the experimental arm had an end of trial interview. The factors influencing capability, opportunity, and motivation to adhere to ENeRgy with supporting evidence (patient quotes) are reported in the Supporting Information, *Data* S2.

In summary, to engage with ENeRgy patients had to perceive benefit; improvement in energy levels, increased physical or social activity, improved food intake, weight gain or, for one patient, an expectation of improved survival. For 10 of the patients, ENeRgy was enjoyable and restorative. However, only some of these patients reported improvement in activity, physical strength, oral intake, or weight. Perception of benefit, such as a sense of achievement, knowing what to do, a sense of control, or hope of improvement, could motivate adherence. Family members and carers also influenced ability to and willingness to adhere to ENeRgy. The four patients who did not report benefit ranged from mildly resistant to non-adherent. These patients revealed that ENeRgy can have an unintended consequence of raising awareness of progressing disease and impending death.

**Table 4** Exploratory endpoints examining patient reported outcomes of quality of life

| | | Experimental arm | | Control arm | | P | | Experimental arm | | Control arm | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | Median (IQR) | n | Median (IQR) | | | n | Median (IQR) | n | Median (IQR) | |
| **Overall QoL** | Baseline | 23 | 66.7 (50–83.3) | 22 | 50 (45.8–70.8) | | **Dyspnoea** | 23 | 50 (16.7–66.7) | 22 | 33.3 (16.7–70.8) | |
| | Midpoint | 18 | 75.0 (50–83.3) | 16 | 50 (50–66.7) | | | 18 | 33.3 (29.2–54.2) | 16 | 33.3 (16.7–62.5) | |
| | Endpoint | 16 | 66.7 (50–83.3) | 13 | 66.7 (50–66.7) | | | 16 | 50 (33.3–66.7) | 13 | 33.3 (16.7–41.7) | |
| | Difference | 16 | 0.0 (−16.7–12.5) | 13 | 0.0 (−16.7–16.7) | 0.846 | | 16 | 8.3 (−16.7–16.7) | 13 | 0.0 (−16.7–16.7) | |
| | Difference % | 16 | 0.0 (−20–18.8) | 13 | 0.0 (−22.5–33.3) | | | 16 | 10 (−33–100) | 13 | 0.0 (−50–75) | 0.589 |
| **Physical** | Baseline | 23 | 88.9 (66.7–100) | 22 | 83.3 (66.7–100) | | **Insomnia** | 23 | 33 (0.0–66.7) | 22 | 33.3 (0.0–33.3) | |
| | Midpoint | 18 | 88.9 (77.8–100) | 16 | 88.9 (77.8–100) | | | 18 | 33.3 (0.0–41.7) | 16 | 0 (0.0–33.3) | |
| | Endpoint | 16 | 83.3 (66.7–100) | 13 | 88.9 (83.3–100) | | | 16 | 16.7 (0.0–66.7) | 13 | 0 (0–0) | |
| | Difference | 16 | 0.0 (0.0–8.3) | 13 | 0.0 (0.0–11.1) | | | 16 | 0 (0–0) | 13 | 0 (−16.7–16.7) | |
| | Difference % | 16 | 0.0 (0.0–9.4 | 13 | 0.0 (0.0–18.3) | 0.268 | | 8 | 0 (−37.5–75) | 13 | −100 (−100 to-75) | 0.92 |
| **Emotional** | Baseline | 23 | 100 (83.3–100) | 22 | 100 (83.3–100) | | **Appetite** | 23 | 0 (0.0–33.3) | 22 | 33.3 (0.0–66.7) | |
| | Midpoint | 18 | 100 (95.8–100) | 16 | 100 (66.7–100) | | | 18 | 16.7 (0.0–66.7) | 16 | 33.3 (0.0–58.3) | |
| | Endpoint | 16 | 100 (100–100) | 13 | 83.3 (83.3–100) | | | 16 | 16.7 (0.0–33.3) | 13 | 0 (0.0–33.3) | |
| | Difference | 16 | 0.0 (0.0–16.7) | 13 | −16.7 (−16.7–0.0) | | | 16 | 0 (0.0–25) | 13 | 0 (−33–0.0) | |
| | Difference % | 16 | 0.0 (0.0–20) | 13 | −16.7 (−16.7-) | 0.006 | | 16 | 0 (−50–25) | 13 | −50 (−100–0.0) | 0.268 |
| **Pain** | Baseline | 23 | 33.3 (16.7–66.7) | 22 | 33.3 (16.7–54.2) | | **Nausea** | 23 | 0 (0.0–33.3) | 22 | 0 (0.0–33.3) | |
| | Midpoint | 18 | 33.3 (16.7–70.8) | 16 | 16.7 (0.0–33.3) | | | 18 | 0 (0.0–66.7) | 16 | 0 (0.0–25) | |
| | Endpoint | 16 | 33.3 (16.7–66.7) | 13 | 16.7 (0.0–41.7) | | | 16 | 0 (0.0–33.3) | 13 | 0 (0.0–33.3) | |
| | Difference | 16 | 0.0 (−16.7–0.0) | 13 | 0.0 (−16.7–16.7) | | | 16 | 0 (0.0–0.0) | 13 | 0 (0.0–0.0) | |
| | Difference % | 13 | 0.0 (−58.3–0.0) | 13 | 0.0 (−100–50) | 0.714 | | 16 | −66 (−100–0.0) | 13 | 0 (−100–0.0) | 0.812 |
| **Fatigue** | Baseline | 23 | 50 (16.7–66.7) | 22 | 33.3 (16.7–70.8) | | **Constipation** | 23 | 0 (0.0–33.3) | 22 | 33.3 (0.0–66.7) | |
| | Midpoint | 18 | 33.3 (29.2–54.2) | 16 | 33.3 (16.7–62.5) | | | 18 | 16.7 (0.0–33.3) | 16 | 0 (0.0–33.3) | |
| | Endpoint | 16 | 50 (33.3–66.7) | 13 | 33.3 (16.7–41.7) | | | 16 | 0 (0.0–0.0) | 13 | 33.3 (0.0–33.3) | |
| | Difference | 16 | 8.3 (−16.7–16.7) | 13 | 0.0 (−16.7–16.7) | | | 16 | 0 (−25–0.0) | 13 | 0 (−16.7–16.7) | |
| | Difference % | 16 | 10 (−33–100) | 13 | 0.0 (−50–75) | 0.449 | | 16 | −100 (−100–16.7) | 13 | 0.0 (−100–0.0) | 0.714 |

**Table 5** Adverse events

| AE type | Experimental arm (*n* 23) | Control arm (*n* 22) |
|---|---|---|
| **AE relating to ONS** | **9** | **N/A** |
| Description | - Flatus/gurgling from stoma<br>- Flatulence/stool frequency<br>- Flatulence/gurgling from bowel<br>- Flatulence and abdominal cramps<br>- Flatulence<br>- Nausea ×2<br>- Diarrhoea<br>- Overactive stoma | |
| **AE related to cancer** | **9** | **12** |
| Description | - Pressure sore<br>- Chest infection ×2<br>- Sub-hepatic haematoma<br>- Intrahepatic bleed<br>- Oesophageal bolus obstruction (tablet)<br>- Falls (recurrent)<br>- Admission to hospice-reduced mobility<br>- Duodenal obstruction | - Deep vein thrombosis<br>- Hypercalcaemia<br>- Fall ×3<br>- Chest infection ×2<br>- Delirium<br>- Rectal bleeding<br>- Pathological femur fracture<br>- Pressure sore<br>- Dysphagia |
| **AE unrelated to cancer** | **2** | **7** |
| Description | - Urinary tract infection<br>- Diarrhoea and vomiting | - Tooth abscess<br>- Atrial fibrillation ×2<br>- Cardiovascular complication<br>- Diarrhoea<br>- Oral antibiotics for skin wound<br>- Diarrhoea and vomiting |

## Discussion

Our findings demonstrate that delivering and testing a rehabilitation programme incorporating exercise and nutritional advice/supplementation, delivered in an outpatient setting to people with incurable cancer, is feasible. This trial recruited ahead of schedule and target, with an acceptable attrition rate in the setting of advanced cancer. The trial was not powered to assess the effects on nutritional, functional or quality of life outcomes, but encouraging changes in emotional functioning were observed, echoed by our qualitative findings. Our health economic analyses were also encouraging. There is a strong belief that rehabilitation should be an optional therapy for the management of people living with incurable cancer, yet trials supporting this viewpoint are scarce. The present trial provides a foundation for larger trials to assess the efficacy of such an approach.

There is limited similar research for comparison; however, two studies are notable. Naito and co-workers completed a single arm trial examining a multimodal intervention (exercise and nutrition) in 30 elderly patients with lung or pancreatic cancer (NEXTAC-ONE).[30] They demonstrated feasibility, and a randomized phase two trial is underway to further assess this approach.[31] Edbrooke and co-workers undertook a randomized trial assessing exercise and behavioural change strategies in 92 patients with inoperable lung cancer.[32] No improvement in exercise capacity was observed (primary outcome), but quality of life improved. These trials, along with the present trial, are well aligned with recommendations by ESMO,[3] ASCO,[4] and the UK National Institute for Clinical Excellence (NICE) for the care of people with incurable cancer. However, a rehabilitative approach, integrated into routine care, remains the exception rather than the norm. In the present study, the paradigm and design were informed by our previous work in cancer cachexia where the importance of a multimodal approach including exercise and optimal nutrition is advocated. Cancer cachexia remains the cause of death in approximately half of patients with cancer, and the combination of nutritional and functional deficits acts synergistically with devastating consequences. Previous work has focussed on uni-modal exercise approaches to rehabilitation with scarce attention to nutritional care scarce. Optimizing nutritional care alongside physical function may serve to optimize rehabilitative potential but also address cachexia as exercise itself has an anti-inflammatory effect. It is hoped that future work will elucidate this.

A key strength of our trial is the embedded qualitative analysis. Feasibility trials often do not progress to efficacy trials due to a lack of encouraging effects on exploratory endpoints, and as such, interventions may seem ineffective. However, we would argue that in feasibility trials, with modest sample sizes, it is unrealistic to expect a plethora of encouraging exploratory endpoint results. Richards and colleagues argue that 'Applying mixed methods integration techniques to data or findings from studies involving both RCTs and qualitative research can yield insights that might be useful for understanding variation in outcomes, the

mechanism by which interventions have an impact, and identifying ways of tailoring therapy to patient preference and type', and we agree.[33] The qualitative findings demonstrated the positive impact of the intervention and suggest continuation to a larger trial is worthwhile and will help refine aspects of the trial design. There are limited qualitative studies conducted as part of quantitative clinical trials in cancer rehabilitation; however, Edbrooke and co-workers are to be commended for assessing the patient experience of their exercise intervention,[34] as part of their clinical trial.[32]

The Health Economic Analysis undertaken suggested that the rehabilitation intervention was cost-saving compared with the control group. We focussed on the costs to the NHS, and community care with some indication of costs to the patients such as travel costs. One potential reason for the cost saving was that the care provided replaced or prevented community healthcare needs. It may have been due to patients having additional attention to their wider symptom control needs (e.g. pain management) or indirect psychological support from the trial team. The Health Economic Analysis is an important part as even if a rehabilitation intervention proves to be efficacious, excess costs may prohibit wide spread integration into health care. Cost-effectiveness analyses may therefore support widespread integration.

The trial had several limitations including the sample size. This was small however in terms of a feasibility trial it was reasonable; however, any definitive conclusions on efficacy cannot be drawn. Further the sample size was also underpowered for health economic analysis, particularly for estimation of costs and this will need further evaluated in any larger trial. We also acknowledge that the heterogeneous sample (age, tumour type, etc.) is a limitation. It was also difficult to standardize background care to ensure both arms received similar care with the exception of the rehabilitation intervention. This latter point is key, and we cannot rule out that improvements in emotional functioning seen in the intervention arm were as result of contact with trial staff rather than the intervention per se. Such aspects are difficult to disentangle yet represent key considerations in future trial design. We also acknowledge that while the intervention targeted physical function and nutrition, we did not quantify degree of cancer cachexia or incorporate specific measures of body composition (lean mass assessment) or measures of muscle function (e.g. hand grip strength). Rather, we focussed on generic measures of function (physical activity) and quality of life but accept that the former parameters would be of interest. Further, characterizing cachexia stage of participants at enrolment, in future trials, would be of interest.

## Conclusion

A rehabilitation intervention targeting exercise and nutrition, in people with incurable cancer, is feasible and has potential benefits in terms of emotional function, motivation, capability attitudes, and costs. The trial was feasible and provides sufficient support for progression to a larger trial to assess efficacy. Such a trial, ENeRgise, is in development and, along with similar trials, will serve to inform rehabilitation interventions in people living with incurable cancer.

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## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Data S1.** Cost effectiveness plane.
**Table S1:** Mean cumulative costs per patient at study end point for NHS, community care and travel.
**Table S2:** Expected Value of Perfect Information (EVPI) per person.
**Table S3:** Expected value of perfect parameter information (EVPPI).
**Table S4:** CRFs Start point-, Midpoint-, Endpoint Assessment.
**Data S2.** Supporting information.
**Data S3.** Supporting information.

## Conflict of interest

B.L. has received honoraria and consultancy fees from Helsinn, Artelo and XBiotech. R.S. has received honoraria and consultancy fees from Helsinn and Novartis. M.F. has received honoraria and consultancy fees from Pfizer. C.H., H.B., D.B., J.C., K.D., E.D., V.G., C.G., P.H., E.H., J.H., A.L., M.M., L. W., and S.T. have no conflicts of interest.

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