Protocol

Rapid evaluation of the COVID-19 pandemic response in palliative and end of life care: national delivery, workforce and symptom management (CovPall)

Improving palliative care for people with COVID-19 by sharing learning

This protocol has regard for the HRA guidance and order of content

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1.0 Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date: 29/05/2020.

…… ……

Name (please print):

……

Position: ……..Vice Principal (Research)……

Chief Investigator:

Signature: Date:

29/05/2020

Name: (please print):

Irene Higginson.

2.0 Key Study Contacts

Chief Investigator	Professor Irene J Higginson
Sponsor	King's College London and King's College Hospital NHS Foundation Trust
Funder(s)	This research was supported by Medical Research Council grant number MR/V012908/1. Additional support was from the National Institute for Health Research (NIHR), Applied Research Collaboration, South London, hosted at King's College Hospital NHS Foundation Trust, and Cicely Saunders International (Registered Charity No. 1087195). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
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3.0 Study summary

Note that the components of the study that relate to WP2, which require HRA approval are highlighted in yellow. Information about WP1 is provided for context and will be used to understand the nature of services taking part in WP2.

Study Title	**Rapid evaluation of the COVID-19 pandemic response in palliative and end of life care: national delivery, workforce and symptom management (CovPall)**
Short title	CovPall: Palliative care for those with COVID-19
Study Design	Observational study with two main work packages (WPs) *WP 1*: Online survey of palliative care providers, with in-depth qualitative case study of sampled providers. *WP 2*: Cohort study of people with COVID-19 receiving palliative care input, with data collected at 4 time points, at first assessment (baseline, T0), 24 hour follow-up, ideally twice, but this will depend on survival (T1, T2), and then at death or discharge (D or Di). WP1 and WP2 are run quickly, (phase I) and analysed. Then both WP1 and WP2 are repeated 6-8 weeks later (phase II), when case studies are added, to gauge key changes.
Study Participants	*WP1*: Clinical leads or other staff of palliative and hospice care services including: palliative care teams in acute hospitals, in-patient hospices/palliative care wards and palliative care community services providing care in peoples own homes and supporting care homes, usually for adults and children *WP 2*: People with COVID-19 receiving any form of palliative care input to their care, of services who participate in WP1.
Planned Size of Sample	The analysis initially will be largely descriptive, with some analytic components. Our sample size in this observational study of the 'natural experiment' of services and treatments changing in response to COVID-19 seeks to balance precision, feasibility and speed. *WP 1*: Targeted invitation to participation to providers of specialist palliative and end-of-life care services in the UK, we estimate responses from 390 services (60% response), ~130 inpatient hospices, 130 hospital palliative care teams, 130 home care teams. Subgroups of this size will give sufficient to detect differences with effect sizes of 0.35, using chi squared ($p<0.05$, df=5, power 80%). We expect a similar level of response from our European and international partners. *WP 2*: This will yield much information to characterise the patients who have COVID-19 and their needs. We will collect pseudonymised data from 200 UK

	patients. Team will extract data retrospectively from their medical records and/or collect it prospectively at baseline. 80 patients with follow up data are needed to detect a difference of 5 points on IPOS (SD=6) between two groups (80 percent power, two-sided 0.05 significance level, mean MCID, SD based on previous research). It will also allow us to identify clear subgroups and actual mean and SDs to enable us to develop hypotheses and sample size calculation for the future. 9-11 patients per service from 20 services (we already have 26 potentially interested), would give us baseline data on 180-220 patients, follow up data on 80-100 (allowing for 50-60% attrition from those who die too quickly to give more than baseline or baseline plus T1, estimate based on audit in one service). Analysis of the above will inform hypotheses, sample size estimates, case studies when WP1 and WP2 are repeated.
Milestones	Month 1: phase I commences - pilot questionnaires and case report forms, build data bases and complete rapid ethical approval, formalise patient, public, policy / service engagement for WP1 Month 1-2: baseline online survey of palliative and end of life care services opens for 4 weeks for WP1 Month 1-2: multicentre cohort study of symptoms, treatments and outcomes opens, target 200 patients recruited, open for 4 weeks for WP2 Month 2-3: early report of findings from WP1 and WP2 in phase I (e.g. via newsletter/early report) of best practice in services, and symptoms and management, policy and clinician engagement and dissemination to improve guidance, practice, service response and care, planning for phase II. Month 4-7: modify as needed, revise protocol and commence phase II to repeat survey and cohort study, to understand time trends and practice changes, rapid case studies identified and conducted Month 8-12: analyse combined data from phase I and phase II, assess changes, complete case studies, consult on findings and report
Planned Study Period	12 months.
Research Question/Aim(s)	The aim of this study is to evaluate the palliative care and end-of-life care response to COVID-19 in terms of services, workforce and symptom management to provide rapid clinical and policy guidance to optimise the response of palliative care clinicians and services to the COVID-19 pandemic.
Study Steering Committee	We establish a Study Steering committee comprised of key partners, experts, policy makers (public health England, NHS England, charities) and patients and

	the public, with an independent chair. This group will review the plans and results as they emerge and advise on all aspects including the dissemination.
Patient and Public and Stakeholder Engagement	Patient, Public and Stakeholder Engagement is integrated throughout the project. Our plans have developed in direct response to Public and Patient engagement via our virtual fora of the Cicely Saunders Institute.

4.0 Funding, sponsorship and study governance

This study has been funded under competitive competition by Medical Research Council grant number MR/V012908/1. Additional support was from the National Institute for Health Research (NIHR), Applied Research Collaboration, South London, hosted at King's College Hospital NHS Foundation Trust, and Cicely Saunders International (Registered Charity No. 1087195). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

The sponsor of the research is King's College London and King's College Hospital NHS Foundation Trust.

Funder and partners have an agreed contract for this research which sets out the role and responsibilities of both parties.

The study is coordinated on a day to day basis by the Chief Investigator, with regular scheduled meetings with study investigators and researchers. Meetings to discuss the research with the funders take place at regular intervals.

5.0 Background

5.1 Lay summary

The COVID-19 pandemic is placing an unprecedented strain on health services, with an estimated 1-4% of people dying from this new disease. Some of the symptoms, such as breathlessness, fever, agitation and pain, are very distressing. But in this new disease these symptoms are not well understood. Palliative care services are adapting rapidly to this situation, but in different ways, not knowing what is best.

This research aims to rapidly evaluate the palliative care response in COVID-19 to improve care in the future. There are two main components, called work packages, to the research.

Work package 1 will survey, UK wide and international, palliative care clinical leads in different services, about their changes in practice, how they use the workforce and volunteers and what symptom management they are using. Later, we will collect some more detailed information from a small number of services through interviewing them.

Work package 2 collects data about patients' symptoms, how they change over time, and the effects of treatments.

We will collect this information immediately and quickly (phase I), and then repeat the data collection after 6-8 weeks (phase II) to understand how practice is changing. We involve patients, families, the public, policy makers and services in all stages of the research and will release early findings to them, to help catalyse an effective response.

5.2 Why this research is important and urgent

COVID-19 is a new disease that is pandemic. Although mild in 81% cases, in ~19% COVID-19 is severe, with overall case fatality ratio estimated between 1-4%.(1) Currently, UK case and deaths are escalating. In north Italy excess mortality is estimated at 200-400% for March.(2) People with pre-existing morbidities, especially heart disease and hypertension have higher case fatality ratios.

To date efforts have focussed on preventing infection, understanding critical care management, patient escalation, treatments for COVID-19. The palliative care response has risked being overlooked,(3-6) although a survey of Italian hospices provided early evidence.(7) Palliative care services are adapting rapidly, but in different ways.

Knowledge gap: There is an urgent need to evaluate the palliative and end of life care response, to understand how it can contribute to health and care delivery in COVID-19, what workforce or volunteer deployment is optimal. It also imperative to identify challenges (e.g. shortages in medicines or equipment, such as syringe drivers) and innovations.

Symptom management in palliative care is currently based on adapting best practice in other end of life conditions to COVID-19 patients and single reports.(8-12) There is very limited evidence about the symptoms experienced in patients with COVID-19 who are very ill or dying. The best evidence is a single case series in a hospital setting,(13) with no evidence on which settings have highest need, what treatments are used, or their effects. Such information is vital and urgently needed to enable

better planning and anticipating clinical management, especially as the numbers needing palliative care are increasing.

5.3 What is already known

Dying with and from COVID-19

COVID-19 is a new disease caused by the novel coronavirus SARS-CoV-2. The first case was identified in China in late 2019, but is now a global pandemic.(14, 15) The number of cases, and deaths, in most countries are exponentially escalating with estimates on 13 April of almost 2 million cases worldwide and 120,000 deaths. COVID-19 causes mild or uncomplicated illness in 81% of patients and in around 19% of patients, it causes severe illness needing hospitalisation(16). The overall case fatality rate of COVID-19 is estimated by the World Health Organisation as 3.4%(17),although this is difficult to know with certainty as the denominator is unknown due to many of those who are mildly symptomatic not being tested, and commonly it ranges 1-4%.(1) Currently figures often do not include community deaths, which in other countries have led to much higher number of deaths.(2)

There are several diverse risk factors for those dying with or from COVID-19. There is a steep increase in mortality in older people with COVID-19(18), although this may well also be confounded with comorbidities. Those who die are more likely to be male, and more likely to have a comorbidity such as hypertension, diabetes, cardiovascular disease, or chronic lung disease(19).

Why is palliative care important?

An Italian survey showed that palliative care could be an integral part of disaster management in people with COVID-19, which should be flexible and innovative to meet the rapidly rising need (7). However, the overall management of the needs of people with COVID-19 are likely to be jeopardized by public health prioritisation, resource limitations and public expectations for reallocation of healthcare resources towards intensive care departments. There is little evidence on what palliative care services can offer during any public health emergency, especially as most emergencies are in low-income countries with little or no palliative care. Evidence from the SARs epidemic however found that dealing with a novel viral epidemic creates spiritual and psychosocial issues similar to those encountered in a palliative care practice. They concluded that palliative care workers would do well to be aware of such issues and act proactively when such epidemics arise(20).

The potential contribution of palliative care

We know that those people with COVID-19 who develop severe or critical disease usually experience it for 3 - 6 weeks. The time from onset of symptoms to the development of severe disease (including hypoxia) is usually 1 week. Among patients who have died, the time from symptom onset to outcome ranges from 2 - 8 weeks.(21) Symptoms include: breathlessness, fever, malaise, myalgia, fatigue, and continuous cough, but have also been reported to include loss of sense of smell and taste (usually the milder cases), diarrhoea, vomiting, headache, abdominal pain. Breathlessness was the most common symptom in patients with COVID-19 needing ICU admissions and in non-survivors of COVID-19(22). Later stages of the disease include pneumonia, acute respiratory distress syndrome (ARDS) and “cytokine storm”. It is also very distressing for patients and families, as patients are often isolated and families cannot visit.

Thus patients dying with or from COVID-19 experience a high burden of symptoms that need to be addressed to gain high-quality end-of-life care. People dying during this pandemic, can be dying from COVID-19, where this is the main cause of illness, or with COVID-19 where they already have pre-existing palliative care needs perhaps through complex co-morbidities or other life-limiting disease. Standard end-of-life care measures, such as focused symptom control, including the need for palliative sedation for refractory symptoms, are paramount.

Palliative care services have a major part to play in managing the care of those with, and dying from, COVID-19. This may include direct care and consultancy services, particularly where there may be a health care workforce under pressure caring for contagious patients with a high symptom burden. Recommendations need to be simple and clear as many clinicians have been redeployed from outside their area of specialty and are working in unfamiliar teams(23). Staff may also have returned to work from retirement, or have less recent clinical experience. Pharmacological treatments are likely to be challenging due to limited drug availability, and palliative care expertise important in determining innovative and appropriate solutions. Palliative sedation may be paramount in this patient group due to refractory dyspnoea, delirium, and possible haemoptysis. Issues such as dementia may compound the problems managing these symptoms. Symptom management in palliative care is currently based on adapting best practice in other end of life conditions to the best of our ability to COVID-19 patients, but there is little evidence to guide these practices.

A recent rapid review of the role and response of palliative care in epidemics and pandemics concluded that hospice and palliative services have an essential role in the response to COVID-19 by: 1) responding rapidly and flexibly; 2) ensuring protocols for symptom management are available, and training non-specialists in their use; 3) being involved in triage; 4) considering shifting resources into the community; 5) considering redeploying volunteers to provide psychosocial and bereavement care; 6) facilitating camaraderie among staff and adopt measures to deal with stress; 7) using technology to communicate with patients and carers; 8) adopting standardised data collection systems to inform operational changes and improve care (24).

5.4 The contribution of this research

The findings from this study will help the Public Health Response to the COVID-19 pandemic.

This project rapidly delivers (preliminary report at 1 month, main report at 2 months), in response to the urgent need:

1. Mapping service innovations, workforce and volunteer deployment, use of telehealth/consultation,(25) how these work in different settings, developed by palliative care services/ hospices
2. Impacts of these innovations on care for patients, communities and families/those important to them, on local hospitals and services; how these support different patient groups, including socioeconomic groups, cultures/ethnicity
3. Key facilitating components and barriers, including equipment availability (e.g. syringe drivers), staff mix, integration etc.
4. Understanding the different groups of people affected by COVID-19 who need palliative care

5. Symptom prevalence, trajectories, treatments, and symptom management effectiveness in patients dying with COVID-19.

The repeated surveys and cohort data after ~2 months in phase II enable further evaluation of practice, on what has and hasn't worked, supplemented by case studies.

This will further inform:

a. Health care and voluntary sector delivery response: it will identify the optimal ways in which palliative and end of life care services, including those in the voluntary sector, can help the response, reduce unnecessary resource use in hospitals or other settings, and how hospices may be best repurposed
b. It will provide a better evidence-based guide to effective symptom management, that can quickly be incorporated into guidance for all settings.
c. It will help improve the management in community and non-healthcare settings, such as where palliative care is supporting care homes.

Our dissemination plan will release first results (from phase I) after WP1 is completed at around 2-3 months into the project (see timeline), for WP2, at 3 months. We will conduct a mid point analysis during the study to determine whether there are emerging findings, which we should report. These will be reporting to the study steering committee. Phase II will give more reflective and larger analysis where it will be possible to collect additional data and conduct case studies. This will help also if the pandemic/epidemic risks returning.

The final analysis and report (12 months) will also provide a blueprint for the management in future COVID-19 or similar epidemics/pandemics.

Unique addition to knowledge

We have completed a rapid systematic review of palliative care responses during pandemic/epidemic situations. Of the 10 studies, only one was European (Italy, we are co-authors), one North American (a simulation) and the rest Asian or African.(24) There is a dearth of information on palliative care in pandemics, despite the UK leading internationally in palliative care quality.(26) Evidence stresses that palliative and end of life care services are essential in pandemics, and that systematic data collection is crucial. This proposal directly responds to this gap.

Our case series identified some symptoms this cohort of patients suffer,(13) but not how to palliate them effectively. Further, we need to better characterise the cohorts, including those dying directly from COVID-19, and others with pre-existing advanced illness plus COVID-19, where existing morbidities contribute to symptoms. Understanding these would enable better targeted clinical guidelines. These are needed quickly. We have partnered with colleagues and policy makers across the UK, via the European Association for Palliative Care, and in Australia. All tell us that this proposal is unique, timely and urgent.

Without this information, we risk suboptimal services with some services reinventing the same wheel, while others do nothing. There is a risk of using inappropriate treatments, inadequate or unnecessary doses of limited drugs, and failing to plan appropriately to ensure that those who die with COVID-19 have the most comfortable death possible. Coordinated national data collection

would avoid hospices and palliative care services doing similar things in isolation, and better channel individual efforts to the national response.

6.0 Project plan

6.1 Aims:

The aim of this study is to evaluate the palliative care and end-of-life care response to COVID-19 in terms of services, workforce and volunteer deployment and symptom management to provide rapid clinical and policy guidance to optimise the response of palliative and end of life care services and clinical care to the COVID-19 pandemic.

This will be delivered through two inter-related work packages (WP).

WP1. Aims to map and understand the response of specialist palliative care providers and hospices to COVID-19 including their workforce and volunteer deployment, service and technology innovations, clinical policies and practices, challenges and successes.

WP2. Aims to understand the prevalence and trajectory of symptoms, treatments received and their effectiveness for patients with COVID-19 receiving any form of palliative care support.

The WPs are conducted initially (phase I) and then repeated (phase II) at a later point to understand service and clinical changes. All settings where palliative care is delivered is included.

6.2 Objectives:

This project will rapidly deliver our objectives:

1. Initial mapping of service innovations, workforce and volunteer deployment developed by specialist palliative care services (including hospices, acute hospital and home care providers), including the support in bereavement and for families.
2. The impacts of these innovations on care for patients and support for communities and families, and on local hospitals and services, and for different patient groups, including different socioeconomic groups, cultures/ethnicity and for families/those important to patients.
3. Key facilitating components, challenges and barriers, including equipment availability (e.g. syringe drivers), staff mix, integration with other services etc.
4. Symptom prevalence, trajectories and their relationship to patient characteristics, in particular patients identifying subgroups, e.g. those who are seriously ill or dying from COVID-19, and patients who had multiple co-morbidities or advanced disease who have COVID-19 as well as their existing conditions.
5. Treatments used for different symptoms, baseline and changes in symptom severity (IPOS subscales and individual items).
6. Symptom management effects (as assessed by the relationship between IPOS score changes and particular treatments, for different symptoms) and characteristics associated with different trajectories and outcomes.

6.3 Patient and Public Involvement and Engagement

This proposal developed in response to a recent consultation with our existing patient and public involvement and engagement (PPIE) networks. We received >40 responses via telephone, email and our online forum (www.csipublicinvolvement.co.uk). These identify the challenges for patients, their families, and members of the public, in relation to palliative and end of life care during the COVID-19 outbreak.

From their experiences, PPIE respondents raised concerns in relation to increased symptom burden, use of advance care plans, how care might be 'rationed' and the possibility of compromised end of life care as a result of the COVID-19 pandemic. These concerns informed our plans and highlight the importance of this research to ensure patients, family and public apprehensions are addressed.

Ongoing PPIE is critical to this project's success. We support and where required will train PPIE colleagues in all project stages, following NIHR INVOLVE best practice and the UK National Standards for PPIE. This is included in our budgets.

We invite two PPIE representatives who engaged in the recent consultation to advise on, and, where appropriate, support: (i) ethical and data protection issues / procedures, (ii) study documentation, consent processes, data collection tools, (iii) interpretation and analysis of results, and (iv) dissemination of results, particularly ensuring outputs are accessible for public audiences and reach relevant patient networks.

We engage wider PPIE networks via email, connections and our online forum to ensure we receive feedback throughout from a diversity of patients, families and public members for key project milestones including the interpretation of results and dissemination of outputs.

6.4 Research design

Observational study with two main work packages (WPs)

WP 1: Online survey of palliative care providers, followed by qualitative case studies with a small number of selected providers.

WP 2: Cohort study of people with COVID-19 receiving palliative care input, with data collected extracted from clinical records retrospectively or recorded prospectively at first assessment (baseline, T0), 12-24 hour follow-up, ideally twice, but this will depend on survival (T1, T2), and then at death or discharge (D or Di). This data collection is designed to be consistent with that taking place in clinical practice, so minimises workload.

Both WP1 and WP2 are carried out quickly (phase I) and then repeated 6-8 weeks (phase II) later to gauge key changes.

6.5 Setting

Palliative care is traditionally delivered where ever patients and those important to them are cared for. This includes: acute hospital care, specialist palliative care units and hospices (voluntary and NHS managed), patients own homes/usual place of residence include care and nursing homes and other community settings. All such settings are currently experiencing care of those with COVID-19, and

many have had extensive service reconfigurations, differing across localities, to enable the care of large numbers of those with COVID-19. We plan to collect data in all the main settings where people are receiving such specialist palliative care (either face to face or via a consultation service).

WP 1:

Inclusion criteria: Palliative care and hospice services across the UK and internationally. This will include: voluntary hospices, hospital based palliative care teams, home care/community teams and other services that offer palliative and/or end of life care. The 2019 Atlas from the European Association for Palliative Care (EAPC) lists specialist palliative care services in the UK.(15) Using this and CQC reports of palliative care services and hospices from their inspections we estimate there are 650 hospices and palliative care services relevant to this proposal across the UK. The UK has more palliative care services than most other countries, so therefore we expect the international response will yield a similar number of services. These will be identified via Hospice UK, Marie Curie Care, Sue Ryder Foundation, the directories of hospital based palliative care teams, the EAPC and our personal networks. The umbrella organisations will write to the services for us, with information about the study, and giving the services the link to complete the on-line survey. We will offer all services the opportunity to complete the on-line survey and will aim to include both adult and children's hospices and palliative care services, those in areas with high and low prevalence of COVID-19, and also different socioeconomic characteristics, ethnicity and culture.

Exclusion criteria: not a palliative care/hospice/end of life service, e.g. having no members of staff with specific expertise/training in palliative care.

WP 2:

Services participating in WP1 from the UK, able to collect information on ≥10 patients in their care. We aim to recruit ~20 services across settings (hospital, community, voluntary hospice), and areas with different cultural/ethnic and socioeconomic diversities.

Outline agreement/interest to participate has already been reached with 26 services across regions in England, Wales and Scotland. This is more than we need, but we anticipate that some services may not be able to collect data in practice, and so would drop out. We will further sample from services responding to the survey in WP1 as required aiming, where possible, for geographical representation across the UK, of those with different proportions of COVID-19 detected, for variety in socio-demographic factors, and in-service provision types.

WP1 is open to palliative care services and hospices across Europe, via our partner the EAPC, and potentially Australian Palliative Care Services. Because of this we have approached the university of the Chief Investigator, King's College London (KCL), for ethical approval for WP1 to allow international data collection. We obtained ethical approval from KCL Research Ethics Committee on the 21st of April 2020 (LRS-19/20-18541) and have launched the WP1 on-line survey. For international data collection in WP1 we are recruiting participating services only via umbrella/gatekeeping organisations (such as EAPC, and potentially national palliative care organisations, such as the German Palliative Care Association) who would email their membership with information about our study and a link to complete the survey. The subsequent qualitative case studies will only be selected from survey respondents in England, but with variability as to

service provider and region in England as well as survey responses regarding experience of caring for those with COVID-19, those from minority ethnic communities, and their responses to the pandemic.

WP2 is being conducted in collaboration with Australia and New Zealand Rapid collaboration, who are planning an audit collecting some similar but smaller data sets. We will discuss our findings with them. It is already is of interest to colleagues in Germany, Ireland, Italy and Belgium, which would allow for greater international comparison. We propose to use some of the same symptom assessment measures as the Rapid collaboration, to allow our results to be contrasted with theirs, and in the future possible meta-analysis. If these countries are interested in taking part in our study, we will encourage them to seek local / national ethical approvals.

6.6 Participants

WP1
Survey Inclusion criteria: Hospice / palliative care medical directors/clinical leads or their nominees, when not available lead nurse or other.

Exclusion criteria: No lead or delegate available.

Case study participant inclusion criteria: Hospice/palliative care medical directors/clinical leads or their nominees (e.g. respondents to the survey), who will then suggest other potential informants within their service which may include other lead clinicians (across different professional backgrounds), service managers, clinical staff or volunteers.

Exclusion criteria: Patients of the service, or their family carers.

WP2
Inclusion criteria: Consecutive patients supported by the participating palliative care services (including remote consultation), with clinically diagnosed and/or test confirmed COVID-19 diagnosis. This will include patients with and without pre-existing progressive conditions.

Exclusion Criteria: Patients who are <18 years old.

6.7 Sample size

Our sample size in this observational study of the 'natural experiment' of services and treatments changing in response to COVID-19 seeks to balance precision, feasibility and speed.

WP1:

Is largely descriptive yielding rich information. The EAPC atlas and CQC reports suggest ~650 services appropriate to this study in the UK. We aim is to reach as many across the UK as possible to complete the survey. A response rate at 60%, yields 390 services, ~130 inpatient hospices, 130 hospital palliative care teams, 130 home care teams. Subgroups of this size (>105) will detect differences with effect sizes of 0.35, using chi squared ($p<0.05$, df=5, power 80%). We expect a similar level of response from our European and international partners.

For the follow-up qualitative case studies we will sample from these settings against criteria including geographical representation, service innovations, and socio-demographic factors. We aim

to complete around 3-5 qualitative case studies, each with around 3-10 participants, depending on service size.

WP2:

Has descriptive and analytic elements. We collect data extracted from clinical records retrospectively, and where possible also record it prospectively on 200 patients in the UK. We plan to collect data on 200 patients. 9-11 patients per service from 20 services, would give us baseline data on 180-220 patients, follow up data on 80-100 (allowing for 50-60% attrition from those who die too quickly to give more than baseline or baseline plus T1, estimate based on audit in one service). 80 patients with follow up data are needed to detect a difference of 5 points on IPOS (SD=6) between two groups (80 percent power, two-sided 0.05 significance level, mean MCID, SD based on previous research).(27, 28) This sample size will also allow us to identify clear subgroups and actual mean and SDs to enable us to develop hypotheses and sample size calculation for the future. Univariate and multivariate regression analyses, accounting for patient casemix and service clustering, will explore the associations between treatments given and patient outcomes (symptom control), as in other observational studies.(29, 30) Following the RAPID model developed and tested in Australia(31, 32), we plan to work across the sampled sites to collect data such that each centre only needs to collect information about a limited number of patients as a minimum, to reduce the burden on individual clinical members of staff. In addition, having a larger number of services (~20) each collecting smaller number of patients (~10) the effects of clustering will be limited, reducing the impact on power.(30, 33, 34)

We anticipate this data collection will be with patients referred to or seen by the palliative care team within each setting, with data collection of up to 4 weeks or until a minimum of 10 patient's data have been collected, whichever occurs soonest. If services wish to collect data on more than 10 patients we will support that up to 20 patients in the first exploratory phase, providing collection does not exceed 4 weeks. We recognise the challenges of collecting data on a complete cohort, missing data, and with expected attrition of 50-60% through to death(35).

6.8 Recruitment

WP1:

We will disseminate information on the survey widely through our institutional websites, social media, working with key collaborators (EAPC, Hospice UK, Marie Curie Care, Sue Ryder Foundation), directories of hospital based palliative care teams and our personal networks.

<u>Case study participant recruitment:</u>

Case study participants will be selected purposively by the research team in conjunction with case study sites, identified as people who are able to give rich data on the phenomena under study. Selection will depend on potential participant role (there may only be one person who fulfils a particular role), and identification as someone who has rich data perhaps by virtue of their

experience within the site in caring for people with COVID-19 and nominated by the key contact within the case study site. They would be asked to distribute invitations to the relevant members of staff who then respond to the research team. Reminders will be sent after two weeks if no response is forthcoming. We anticipate interviewing between 3-10 participants per case study site, depending on the size of the site(s) selected

WP2:

The palliative care clinical team within participating sites will identify patients and facilitate data collection on as complete a cohort as possible of those patients who meet the inclusion criteria across a set time period and to an agreed maximum number of patients. Informed consent from patient participants will not be possible given the illness status of the patients, and the likely rapidly deteriorating health status of those who will form the cohort for this study. Therefore, we will ask the direct care team to access this routinely collected data and de-identify it before transferring these data securely to the research team. There will be no breach of confidentiality as the research team will not receive any confidential patient information.

6.9 Data collection

WP 1:

On line survey using REDCap builds on but considerably extends the Italian survey of palliative care directors(7). REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data, it is specifically geared to support online or offline data capture for research studies and similar operations.

Key variables: palliative care services type, location, catchment area, innovations in response to COVID-19, deployment of workforce and volunteers, use of virtual technologies, support for care homes and other settings, bereavement support offered, advance care planning, protocols/recommendations being used for symptom management, challenges, equipment needs, examples of best successes, open comments.

Sites will be encouraged to enter data online directly, but if required they can give the information to a trained interviewer over the telephone or virtual connection (e.g. via Microsoft teams or Zoom) who will enter the data for them. Or they prefer they can be sent the survey as a word document via email to complete and return electronically (e.g. via secure NHS email).

Qualitative case studies involving telephone or video (e.g. using Microsoft Teams, Zoom or similar) interviews with clinical leads of participating services and other nominated informants. The case studies may focus on a specific theme of interest that emerges in the phase I WP1 survey, e.g. use of telecommunications, advance directives, medicines, or on particular services. A topic guide rather than a fixed schedule will guide but not constrain the interviews, ensuring that interviews are driven by participant issues. Interviews will be conversational to aid developing rapport to explore complex and potentially challenging and emotional issues. The topic guide will evolve as categories are

discovered through the interviews and analysis but are likely to include exploration of the service response to COVID-19, the opportunities and challenges experienced, their perceptions of the impact of COVID-19 on their service, and appraisal of their impact on patients and family carers into bereavement care. Interviews may vary in length, but are likely to be around 30 minutes.

WP2:

Data will be extracted from clinical records retrospectively or collected propectively where possible, for individual patients up to 4 time points at 24-hour intervals, reflecting on the previous 12 hours of care, or until the death of the patient if earlier. We acknowledge the high probability of attrition, missing data and/or missing timepoints given the pandemic situation, and will not exclude the patient from the cohort in this situation. To minimise burden on the direct clinical care team we have used routinely collected data where possible. Baseline is determined as first contact with the palliative care team during the current episode of care. This may be on admission to the care setting, or later in the care trajectory.

Data collection procedures will have to be locally adapted to take account of infection control procedures that may affect the ability to collect certain forms of data (e.g. on paper, in the presence of someone with known infection). Where possible clinical teams will enter data directly using password protected bespoke secure study data base (likely to be REDCap as for the survey and Australian study, but Macro is also being considered). Patients will have a unique alpha-numeric code allocated which will identify both the site providing data and where the patient is in their consecutive sequence.

Data collection has been designed to be parsimonious, in line with current NICE guidance(36), available information on COVID-19 core outcome sets(37), and using validated tools such as the IPOS(38, 39)

Table 1 Data collection

Timepoint	Data	Details
BASELINE (T0)	Date and time stamp	
	Setting	ICU, Acute hospital ward, palliative care unit/hospice, emergency department, home, nursing care home, hostel/sheltered accommodation, other (insert details).
	Gender	Male, female, other
	Ethnicity	ONS categories
	Age	Age in years
	Weight/Height	Calculate BMI
	Date of first COVID symptoms	Date
	Date of COVID diagnosis, if known	Date
	Date referred to palliative care	Date
	Postcode	Transform to LSOA to enable linkage to deprivation measure (IMD)

	Smoking currently	yes/no
	Charlson Comobrbidity Index	MI, CCF, peripheral vascular disease, CVA, Dementia, Leukaemia, Cancer, Connective Tissue Disease, Diabetes, Hypertension, Renal disease, liver disease, peptic ulcer disease, COPD, Lymphoma, AIDS.
	Date and time of assessment	Date and Time
	Place of Care	ICU/Acute hospital ward/In-patient hospice/palliative care ward in a hospital /Community hospital/Emergency department /Own home (or of a relative/friend)/Nursing home/Care home/Sheltered accommodation/ Hostel/Community bed (not hospital) /Other
	Australian Modified Karnofsky Performance Scale	Range from 100 (normal) to 10 (comatose or barely rousable).
	Phase of illness	Stable, Fluctuating, Deteriorating, Dying
	Laboratory tests (if available)	D-dimer, Lymphocyte count, Lactic Dehydrogenase, High sensitivity C-reactive protein
	Oxygen therapy	Room air/O2 via nasal prongs or mask/BiPAP or CPAP/ventilated
	IV fluids	Yes, what was received or rate over the last 12 hours
	Temperature	Celsius
	Baseline symptom severity (over the past 12 hours/currently scoring from 0 (not at all) to 4 (overwhelming) based on the validated IPOS measure (28, 40)	Breathlessness, fever, cough, pain, shivering, sore or dry mouth, anxiety, agitation, confusion/delirium, drowsiness, weakness/lack of energy, poor appetite, constipation, diarrhoea, nausea, vomiting, poor mobility, other.
	List of current medications being used to treat symptoms	Medication, symptom indication, dose, frequency, route.
	Open comments	
	Communication with family and friends	Yes, how communication was facilitated No, why communication could not be facilitated
	Participation in other COVID-19 studies	Yes, which studies
T1/T2		
	Date and time of assessment	Date and Time
	Place of Care	ICU/Acute hospital ward/In-patient hospice/palliative care ward in a hospital /Community hospital/Emergency department /Own home (or of a relative/friend)/Nursing home/Care home/Sheltered accommodation/ Hostel/Community bed (not hospital) /Other
	Australian Modified Karnofsky Performance Scale	Range from 100 (normal) to 10 (comatose or barely rousable).
	Phase of illness	Stable, Fluctuating, Deteriorating, Dying

	Laboratory tests (if available)	D-dimer, Lymphocyte count, Lactic Dehydrogenase, High sensitivity C-reactive protein
	Oxygen therapy	Room air/O2 via nasal prongs or mask/BiPAP or CPAP/ventilated
	IV fluids	Yes, what was received or rate over the last 12 hours
	Temperature	Celsius
	Symptom severity (over the past 12 hours/currently scoring from 0 (not at all) to 4 (overwhelming) based on the validated IPOS measure (28, 40)	Breathlessness, fever, cough, pain, shivering, sore or dry mouth, anxiety, agitation, confusion/delirium, drowsiness, weakness/lack of energy, poor appetite, constipation, diarrhoea, nausea, vomiting, poor mobility, other.
	Changes made to medications given to the patient since last assessment	Medication, symptom indication, dose, frequency, route.
	Open comments	
	Communication with family and friends	Yes, how communication was facilitated No, why communication could not be facilitated
D	Death (De) or discharge (Di)	outcome, whether died or discharged, transferred, dates where known
	Place of death or destination on discharge	ICU, Acute hospital ward, palliative care unit/hospice, emergency department, home, nursing care home, hostel/sheltered accommodation, other.
	Symptoms in 12 hours before death or discharge.	Breathlessness, fever, cough, pain, shivering, sore or dry mouth, anxiety, agitation, confusion/delirium, drowsiness, weakness/lack of energy, poor appetite, constipation, diarrhoea, nausea, vomiting, poor mobility, other.
	Changes made to medications given to the patient since last assessment	Medication, symptom indication, dose, frequency, route.
	Free text comment box	

6.10 Data analysis

WP1:

Survey: Descriptive analysis of innovations in services, workforce and volunteer deployment, and their impacts on care and bereavement services; identification of good practice, and sharing of approaches and knowledge. Change in practice, most effective treatments. Bereavement services identified. Hospice and palliative care service characteristics that are associated with most effective changes. How people from different sociodemographic groups and ethnic groups are supported. If

data permit, contingency tables assessed using chi-squared to compare types of responses/challenges/use of technology by key characteristics (e.g. of hospital support teams, services that are NHS or voluntary sector funded).

Qualitative case studies: Data analysis will follow a Framework Analysis approach to facilitate analysis between cases using a matrix approach. Framework analysis facilitates within and cross case pattern matching and has been used in case studies in palliative and end of life care (41-44). The approach involves a systematic process of sifting, charting, and sorting material according to key issues and themes following five key stages: familiarisation, identifying a thematic framework, indexing, charting, and mapping and interpretation. Cross case pattern matching follows to identify thematic factors associated with challenges and successes of the site response to COVID-19 whilst taking account of context. This should provide information on what is working well, and challenges, barriers and strategies for overcoming them. All qualitative analyses will be managed using NVivo™ software.

WP2:

A full statistical analyses plan will be drafted and approved by the study steering committee. Data analysis will be focused on addressing our research aims: describing the characteristics of those receiving palliative care, assessing symptom prevalence at baseline and over time, describing treatments used, and assessing their effect and the outcomes of care.

a) Transform data: calculate Charlson Comorbidity Index; days since symptoms/diagnosis of COVID-19 before baseline; calculate BMI. Characterise the different groups of patients receiving palliative care (e.g. those who are dying from COVID-19, those with severe pre-existing multimorbidity who are dying with COVID-19, and those previously known to palliative care). Categorise medication according to type and symptom target.
b) Understanding and description of missing data to inform analysis of missing data and attrition. We will use the MORECare categorisation of missing data and attrition,(35, 45) as well as data missing not at random, missing at random, missing completely at random, to inform any imputation and sensitivity analysis assumptions.
c) Describe the characteristics of the participant cohort at baseline, and at each timepoint. Continuous/ordinal normally or near normally distributed data will be summarised using means and standard deviations (SD), medians and interquartile ranges (IOR) will be used if non-normally distributed. Total IPOS and subscale scores will be calculated with means and SDs. Categorical data will be described using frequencies and percentages.
d) Understand effects of clustering by centre, and intra-cluster correlation coefficients (ICC) and how these should be adjusted for the analysis
e) Changes in scores over time are estimated, for the whole sample and sub-groups
f) Plots of trajectories of symptoms, grouping patients according to sub-groups, and patterns in changes in symptoms using radar charts and area under the curve.
g) Modelling to track symptoms and medication (e.g. pain and analgesia, anxiety and anxiolytics, fever and antipyretics etc. etc.) and relationship with variables thought to affect outcome (e.g. comorbidities, age, gender etc.) over time using regression analysis adjusted for confounders and any service clustering.

6.11 Risks and Benefits

The research team will draw on their considerable experience in conducting research in this area to ensure a design sensitive to this professional and patient group. We have worked with service teams to discuss the acceptability of the research aims, design and local implementation.

WP1:

Qualitative case studies: Interviews will be organised at a time and place to suit the participants, and conducted by researchers with experience of discussing sensitive topics. Verbal consent will be obtained from all participants in the qualitative case studies. Participants will be sent a copy of the participant information sheet and consent form prior to the interview. If they wish to take part in the study after having the opportunity to ask questions, they will be asked to confirm on the recording that they agree to all the items on the consent form. Regular checks will be made during the interview to ensure participants are happy to continue.

Arrangements will be made to inform participants of support agencies if required. The main anticipated risk is that of becoming unduly distressed whilst discussing issues associated with the extreme challenges of the COVID-19 pandemic. We will work to minimise this risk by conducting the interviews in a sensitive and responsive manner, drawing on our research and clinical experience in this field. We have a clear distress protocol to be followed during the research should any distress be apparent or detected during data collection.

There is also the possibility that participants may disclose information about care which reveals risk or poor practice. If they do, this situation will be discussed with the participant and their views on sharing this information with a senior member of staff sought. Where possible their views will be respected, but if a situation is revealed which severely compromises their own or others health or wellbeing, the researcher will inform the participant that they have a duty to disclose this information to the most relevant person.

WP2:

We have designed this data collection to be feasible in the current circumstances by minimising burden on the direct clinical care team whilst maintaining patient confidentiality. There is no burden

We are collecting individual level pseudonymised patient data that will be securely transferred to the research team at Kings College London via REDcap. This is done by sending via secure email (e.g. NHS mail) each participating service a unique set of 11 randomly generated codes. They use one code per patient about which they enter information. They keep a local record of the details of which patient has been assigned to which code, but this information is not transferred to the research team. The REDcap data base does not include any identifying features, including the name of the service, its region, nor any patient identifiable details.). Obtaining patient consent in the current situation is not feasible therefore we have minimised the dataset to remove any confidential patient information e.g. changed date of birth to age, postcode to LSOA.

These will still be individual level data, albeit pseudonymised, so we will ensure that these data are transferred securely between research sites and Kings College London. Once on the Kings College London server they will be held securely on password protected encrypted files.

Current infection control policies restrict our ability to display posters at the study sites but transparency statements will be made available on the Kings College website and all participating study sites so that patients are informed of this study.

7.0 Regulatory requirements

7.1 Research Ethics Committee (REC) and other Regulatory review & reports

We have already obtained KCL Research Ethics Committee approval for the on-line survey (WP1) (LRS-19/20-18541). Before the start of WP2, a favourable opinion will be sought from HRA / NHS REC for the study protocol, and other relevant documents. This will be under the fast track COVID-19 arrangements. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained.

Annual reports, annual progress reports, and end of study notifications will be the responsibility of the Chief Investigator. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

7.2 Regulatory Review & Compliance

WP2:

Before any site can start collecting participant level data, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. This will require HRA and local research governance approvals for NHS sites with associated capability and capacity assessments.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

7.3 Amendments

If a substantial amendment (as determined by the sponsor, advised by the Chief Investigator) is required to the REC application or the supporting documents, the sponsor will submit a valid notice of amendment to the REC for consideration. Amendments will also be notified to the HRA and communicated to the participating organisations (R&D office and local research team) departments

of participating sites to assess whether the amendment affects the NHS permission for that site. Minor amendments will be notified to the HRA, and with their approval, to participating organisations. Amended documentation or the protocol will be sequentially numbered and dated.

The requirements for amendments may be identified by the research team, participating sites, or funder.

7.4 Protocol compliance

Accidental protocol deviations can happen at any time. They will be adequately documented and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.0 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of The Data Protection Act 2018, the UK's implementation of the General Data Protection Regulation (GDPR), with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

8.1 Confidentiality, data handling and security

Data storage and handling will comply with NHS hospital, participating sites, hospices and University policies. This will include locked storage, password protection, encryption and anonymisation of original data. The key to anonymised data will be kept only on a separate register, and stored separately from all other research records. Data will be stored on secure University or Hospital servers and encrypted, anonymised data files. Data will be stored on a distinct area of a secure server, accessible only by authorised members of the research team, encrypted and password protected.

Interviews may be reviewed by an experienced researcher within the research team for quality assurance purposes and will be digitally audio-recorded only if the participant consents for this to occur. Interviews will be digitally recorded on an encrypted recorder and transferred as soon as possible to a password protected computer. All audio−recordings will be labelled only with participants' alphanumeric codes (names will not be used). Audio files will be uploaded to a secure remote server accessible only to the research team as appropriate. Once this has been done, the audio recording of participants' voices on the recorder will be deleted. In the meantime, the digital recorder will be handled and stored securely.

Transcribers will be authorised providers of such services, and will have signed a confidentiality agreement as part of the contracting process. Transcription accuracy checks will be made. Direct quotations form respondents will only be used in such a way as to ensure anonymity.

8.1.1 Storage, back up and security

Data will be initially stored and backed up using password protected central institutional filestores. Data will be shared only where required, and will be shared secure servers.

Paper data will be stored in locked filing cabinets. The study PI has overall responsibility for the collection and management of data generated by this research. All study investigators will be responsible for completing relevant data and information security training.

8.1.2 Data archiving, preservation and destruction

Data will be archived for 10 years following the end of the project. Data will be stored in King's College London in accordance with GDPR and King's College London guidelines. King's College London's Research Data Management System provides secure long-term storage facilities for datasets of published research with provision of a Digital Object Identifier (DOI) and publication of a metadata record for each dataset. Data will only be made openly available once the publication and dissemination targets of the project as outlined above have been fully met. At the end of the default retention period (10 years) all audio recordings and transcripts will be confidentially destroyed by a secure method, along with anything relating to the identification of participants.

8.2 Indemnity

The study is indemnified by the study sponsor: King's College London, co-sponsor King's College Hospital NHS Foundation Trust.

8.3 Data sharing

An important component is the sharing of data among the collaborators for the benefit of patients and families, for education, research and improving care. To facilitate this, ethical and other agreements with participants will include an explicit clause to share anonymised data that is collected as part of CovPall.

We collaborate as appropriate with other researchers who may be collecting similar data sets in other countries, such as Australia, and will consider sharing anonymised protected data with them and vice versa if it will more rapidly inform the response to COVID-19. At the end of the project, when analysis by the partners is completed, data will be placed in local or national repositories for use by others, according to the permissions granted and the procedures of individual partners.

All publications will include a data access statement that will clarify which data was used and provide details about the availability of data.

9 Dissemination policy

We plan early dissemination to aid the pandemic response. This will be agreed with the study steering group, but we anticipate a first report within 2 months, possibly sooner. We will share data with key policy makers and others as requested / needed.

A report will be prepared for Medical Research Council (MRC), as funders of this research. Additional dissemination is planned at professional and academic conferences and in peer-reviewed journals.

A results summary written for a lay audience will be made available to research participants and the communities and sites from which they are drawn. Oral presentation of the results to the relevant local professional and health and social care communities will be offered.

10 Study Steering group

- Bee Wee, National Clinical Director for Palliative and End of Life Care, NHS England and NHS Improvement (confirmed)

- Julia Verne, Clinical Lead for Public Health England, National End of Life Care Intelligence Network (confirmed)

- Julie Ling, COO, European Association for Palliative Care (EAPC)

- Two Patient and family representatives

- Key charity leads, e.g. Hospice UK/Marie Curie?

Stephen Barclay, lead for East of England NIHR ARC on Palliative and End of Life Care, Professor of Palliative Primary Care

Saskie Dorman, Consultant in Palliative Medicine, Poole Hospital NHS Foundation Trust Bournemouth (confirmed)

Kirsty Boyd, University of Edinburgh

Anthony Byrne, clinical director Marie Curie Palliative Care Research Centre, Cardiff University, honorary Professor, Cardiff University

Andrew Wilcock, Palliative Medicine and Medical Oncology, lead editor of the Palliative Care Formulary, the main guide to palliative care prescribing

Caroline Stirling, Clinical Director for End of Life Care Network for London.

11. References

1. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020.
2. Montagano C. COVID-19: excess mortality figures in Italy. A comparison between official COVID-19 deaths and mortality in Lombardy. Towards Data Science. 2020;https://towardsdatascience.com/covid-19-excess-mortality-figures-in-italy-d9640f411691?gi=cbcfa620700a.
3. Kunz R, Minder M. COVID-19 pandemic: palliative care for elderly and frail patients at home and in residential and nursing homes. Swiss Med Wkly. 2020;150:w20235.
4. Hendin A, La Riviere CG, Williscroft DM, O'Connor E, Hughes J, Fischer LM. End-of-life care in the emergency department for the patient imminently dying of a highly transmissible acute respiratory infection (such as COVID-19). CJEM. 2020:1-4.
5. Arya A, Buchman S, Gagnon B, Downar J. Pandemic palliative care: beyond ventilators and saving lives. Cmaj. 2020.
6. Editorial. Palliative care and the COVID-19 pandemic. Lancet. 2020;395 (10231):1168.
7. Costantini M, Sleeman K, Peruselli C, Higginson IJ. Response and role of palliative care during the COVID-19 pandemic: a national telephone survey of hospices in Italy. Palliat Med. 2020;In Press (preprint at https://www.medrxiv.org/content/10.1101/2020.03.18.20038448v1 DOI: https://doi.org/10.1101/2020.03.18.20038448).
8. Ferguson L, Barham D. Palliative Care Pandemic Pack: a Specialist Palliative Care Service response to planning the COVID-19 pandemic. J Pain Symptom Manage. 2020.
9. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing symptoms (including at the end of life) in the community2020.
10. Borasio GD, Gamondi C, Obrist M, Jox R, For The Covid-Task Force Of Palliative C. COVID-19: decision making and palliative care. Swiss Med Wkly. 2020;150:w20233.
11. Bajwah S, Wilcock A, Towers R. Managing the supportive care needs of those affected by COVID-19. European Respiratory Journal. 2020;DOI: 10.1183/13993003.00815-2020 (on line)
12. Adams C. Goals of Care in a Pandemic: Our Experience and Recommendations. J Pain Symptom Manage. 2020.
13. Lovell N, Maddocks M, Etkind Sea. Characteristics, symptom management and outcomes of 101 patients with COVID-19 referred for hospital palliative care. J Pain Symptom Manage. 2020;(in press).
14. Zhao S, Musa SS, Lin Q, Ran J, Yang G, Wang W, et al. Estimating the unreported number of novel coronavirus (2019-nCoV) cases in China in the first half of January 2020: a data-driven Modelling analysis of the early outbreak. Journal of clinical medicine. 2020;9(2):388.
15. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: towards controlling of a pandemic. The Lancet. 2020.
16. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). International Journal of Surgery. 2020.
17. Mahase E. Coronavirus: covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. British Medical Journal Publishing Group; 2020.
18. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. The Journal of Infection in Developing Countries. 2020;14(02):125-8.
19. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368.
20. Leong IY-O, Lee AO-K, Ng TW, Lee LB, Koh NY, Yap E, et al. The challenge of providing holistic care in a viral epidemic: opportunities for palliative care. Palliative Medicine. 2004;18(1):12-8.

21. World Health Organisation. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 2020.
22. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
23. Fusi-Schmidhauser T, Preston N, Keller N, Gamondi C. Conservative management of Covid-19 patients; emergency palliative care in action. Journal of Pain and Symptom Management.
24. Etkind S, Bone AE, Lovell Nea. The role and response of palliative care and hospice services in epidemics and pandemics: a rapid review to inform practice during the COVID-19 pandemic. J Pain Symptom Manage. 2020;Doi: https://doi.org/10.1016/j.jpainsymman.2020.03.029 (on line).
25. Calton B, Abedini N, Fratkin M. Telemedicine in the Time of Coronavirus. J Pain Symptom Manage. 2020.
26. The Economist Intelligence Unit. The 2015 Quality of Death Index. Ranking palliative care across the world: The Economist Intelligence Unit; 2015.
27. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Birring SS, et al. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. Thorax. 2015;70(9):830-9.
28. Murtagh FE, Ramsenthaler C, Firth A, Groeneveld EI, Lovell N, Simon ST, et al. A brief, patient- and proxy-reported outcome measure in advanced illness: Validity, reliability and responsiveness of the Integrated Palliative care Outcome Scale (IPOS). Palliat Med. 2019;33(8):1045-57.
29. Cafri G, Wang W, Chan PH, Austin PC. A review and empirical comparison of causal inference methods for clustered observational data with application to the evaluation of the effectiveness of medical devices. Statistical methods in medical research. 2019;28(10-11):3142-62.
30. Langhorne P, O'Donnell MJ, Chin SL, Zhang H, Xavier D, Avezum A, et al. Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): an international observational study. Lancet. 2018;391(10134):2019-27.
31. Currow DC, Vella-Brincat J, Fazekas B, Clark K, Doogue M, Rowett D. Pharmacovigilance in hospice/palliative care: rapid report of net clinical effect of metoclopramide. J Palliat Med. 2012;15(10):1071-5.
32. Digges M, Hussein A, Wilcock A, Crawford GB, Boland JW, Agar MR, et al. Pharmacovigilance in Hospice/Palliative Care: Net Effect of Haloperidol for Nausea or Vomiting. J Palliat Med. 2018;21(1):37-43.
33. Dieleman JL, Templin T. Random-effects, fixed-effects and the within-between specification for clustered data in observational health studies: a simulation study. PLoS One. 2014;9(10):e110257.
34. Lancaster GA, Chellaswamy H, Taylor S, Lyon D, Dowrick C. Design of a clustered observational study to predict emergency admissions in the elderly: statistical reasoning in clinical practice. J Eval Clin Pract. 2007;13(2):169-78.
35. Preston NJ, Fayers P, Walters SJ, Pilling M, Grande GE, Short V, et al. Recommendations for managing missing data, attrition and response shift in palliative and end-of-life care research: part of the MORECare research method guidance on statistical issues. Palliat Med. 2013;27.
36. National institute for Health and Care Excellence. COVID-19 rapid guideline: critical care in adults. NICE guideline [NG159]. 2020.
37. Jin X, Pang B, Zhang J, Liu Q, Yang Z, Feng J, et al. Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (COS-COVID). Engineering. 2020.
38. Murtagh FE, Ramsenthaler C, Firth A, Groeneveld EI, Lovell N, Simon ST, et al. A brief, patient-and proxy-reported outcome measure in advanced illness: Validity, reliability and responsiveness of the Integrated Palliative care Outcome Scale (IPOS). Palliative medicine. 2019:0269216319854264.

39. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987;40(5):373-83.
40. Sandham MH, Medvedev ON, Hedgecock E, Higginson IJ, Siegert RJ. A Rasch Analysis of the Integrated Palliative Care Outcome Scale. J Pain Symptom Manage. 2019;57(2):290-6.
41. Walshe C, Chew-Graham C, Todd C, Caress A. What influences referrals within community palliative care services? A qualitative case study. Social Science & Medicine. 2008;67(1):137-46.
42. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess RG, editors. Analysing qualitative data. London: Routeledge; 1994.
43. Walshe C. The evaluation of complex interventions in palliative care: An exploration of the potential of case study research strategies. Palliative Medicine. 2011;25(8):774-81.
44. Walshe CE, Caress AL, Chew-Graham C, Todd CJ. Case studies: a research strategy appropriate for palliative care? Palliative Medicine. 2004;18:677-84.
45. Oriani A, Dunleavy L, Sharples P, Perez Algorta G, Preston NJ. Are the MORECare guidelines on reporting of attrition in palliative care research populations appropriate? A systematic review and meta-analysis of randomised controlled trials. BMC Palliat Care. 2020;19(1):6.