CARer-ADministration of as-needed sub-cutaneous medication for breakthrough symptoms in homebased dying patients: a UK study (CARiAD)

Cariad: sweetheart.
From the Welsh. Derived from "caru" = to love

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Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1	October 2016	Jessica Roberts, Marlise Poolman, Clare Wilkinson, Zoe Hoare, Julia Hiscock	Version 1 was approved by the funder, and detailed the whole CARiAD project (including the work-up phase/expert consensus workshops). The workshops have been concluded and results incorporated in trial processes and materials. Version 2 focusses on the trial (with embedded qualitative study), due to commence October 2017.
	2	June 2017		
	3	July 2017	Jessica Roberts, Marlise Poolman, Clare Wilkinson	Amended in responses to the REC comments

CONTENTS

1. ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DCE	Discrete Choice Experiment
DMEC	Data Monitoring and Ethics Committee
DN	District Nurse
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Healthcare Professional
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trials Number
IPA	Interpretative Phenomenological Analysis
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS R&D	National Health Service Research and Development
NWORTH	North Wales Organisation for Randomised Trials in Health
OOH	Out of hours
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient Public Involvement
RCT	Randomised Control Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SC	Subcutaneous
SOP	Standard Operating Procedure
SSI	Site Specific Information
SPC	Specialist Palliative Care
TMG	Trial Management Group
TSC	Trial Steering Committee

2. BACKGROUND

This project focusses on timely administration of as-needed medication for dying patients being cared for at home, in particular whether lay carer role-extension (to be trained to give as-needed SC injections) is feasible and acceptable in the UK.

Caring for the dying during their last few days of life, in a place of their preference, is an essential part of health and social care. The majority express a wish to die at home (79%), however only half of those achieve this. (1) The likelihood of patients remaining at home often depends on availability of able and willing informal carers. (2) (3) (4) These carers take on numerous care tasks, often including the responsibility of assisting patients to have their oral as-needed medications. The role of carers administering SC injections has proven to be key in achieving home death in other countries. (5)

Pain, nausea/vomiting and restlessness/agitation are common symptoms in the dying. (6) (7) (8) In addition to regular (background) medication, often given via syringe driver, guidelines suggest using additional ('as -needed') medication for symptoms that 'break through'. (9) (10) Dying patients are usually unable to take oral medication; it is most often given as a SC injection by a healthcare professional (HCP), (9) usually a District Nurse (DN).

Medication for breakthrough symptoms is usually prescribed in advance (anticipatory prescribing) and kept in the person's home. Medication administration can be severely delayed by HCPs travel time to the home and/or the non-availability of anticipatory medication in the home. Delays happen even with dedicated out-of-hours (OOH) 'rapid response' nursing services for home-based dying patients. Our local audit revealed long waits (call to OOH service for symptom control to as-needed medication administration by HCP: median=86 minutes, mean=98.56, range=35-167, not including time from administration to onset of action or symptom control). (11) Breakthrough pain, specifically, is usually quick in onset with a median duration of 30 minutes. (12) Long waits mean that pain is often not adequately managed, borne out by the National Survey of Bereaved People (VOICES) finding that pain management is poorer in the home setting than in hospital, hospice or care homes. (1)

CARiAD is about:

- Carers, who are family members or other lay carers looking after their loved one at home; not paid to do this work
- Carers willing to explore all the options they might have to honour their loved one's wish to die at home, even if this might be challenging (as long as they are properly trained and supported in the tasks)
- A legal practice in the UK of carer-administration of medication, including strong painkillers, to patients unable to make decisions for themselves
- A practice that builds on best palliative care, rather than replacing it
- A practice which is not yet routine in the UK and needs careful testing
- Speedier relief of symptoms that 'break through' which are treated with as-needed medication
- Testing whether, in the UK, the carer role can routinely be extended to include training in the administration of SC medication to a dying patient who is unable to swallow their usual medication
- Giving carers the option to be trained, if indeed it is found to be acceptable and feasible in our study

CARiAD is NOT about:

- Background symptoms which are treated by a continuous SC infusion when a patient becomes unable to swallow their usual regular medication
- Pressurising carers to take on the extended role, if that is not right for either the carer or their loved one
- Hastening death, or replacing best quality palliative care from health professionals

a. Rationale

Although carer administration of medication (including strong opioids) is legal and practical, it is not currently part of usual care everywhere in the UK. This practice is much-needed: the Palliative and End of Life Care Priority setting Partnership (PeolcPSP) accorded highest priority to research into the provision of palliative care, including symptom management, outside of working hours to avoid crises and help patients to stay in their place of choice. It noted the information and training needs of carers and families to provide the best care for their loved one who is dying, including training for giving medicines at home. (13) As yet unpublished survey data from the PeolcPSP work, indicates that UK patients are being denied the opportunity to die at home due to lack of access to adequate symptom relief. (14)

Carers across the world embrace this as an option, as evidenced through the published literature as well as evidence from our PPI group consultations. (15) In Australia the practice is well –established (more than 30 years) and highly acceptable. (5) A manualised educational package and evidence-based guidelines are available which could easily be adapted and tested in a UK environment.
Successful carer-administration of as-needed SC medication for breakthrough symptoms in a dying patient is likely to

- improve the quality of experience (and thus increase the likelihood of a 'good death') for the patient who chooses to be at home by providing speedier symptom control and supporting their wish to die at home.
- empower lay carers through the personal fulfilment of having supported a patient's wish to stay at home; increase satisfaction and reduce anxiety and frustration related to poor symptom control
- reduce inappropriate emergency (crisis) admissions due to uncontrolled symptoms and its associated costs. (16) (17)
- free up community staff time to address other needs of patients and families, contributing to sustainability of services.

Capacity to generate new knowledge: This practice appears logical and acceptable in countries such as Australia. However, there are no randomised studies testing carer administered non-oral medication in the last days of life for home-based patients anywhere in the world. (18) This study will provide an exemplar for conducting randomised controlled trails in the last days of life by contributing to the emerging methodological development of palliative care research.

Equipoise is emerging on this topic in the UK. Carer-administration of as-needed non-oral (including SC) medication for breakthrough symptoms in home-based dying patients is practiced in a limited way in some

areas in the UK, and has been for a number of years. For this to be widely available to all carers who are considering supporting a loved one at home, it needs to be tested in a UK environment, with the support of an evidence-based carer education programme and resources. Not all family, carers or patients at home will want to be involved in this practice: the research will help to ascertain this proportion, and how to train/support those who are willing.

How does the existing literature support this project?

A. Carers prioritise rapid symptom control, are willing and able to administer injectable drugs, including controlled drugs such as morphine

- A narrative literature review of family carer perspectives on supporting a dying person at home illustrated the desire of families to provide immediate symptom relief. (19)
- Our review found that caregivers are willing to learn to overcome reservations about administering SC medications. (18) The ability to alleviate their loved ones' symptoms and supporting them to stay at home was of paramount importance.

B. There is an existing evidence-based and tested education package, and medication resources:

- A Brisbane group developed and evaluated an educational package. (5) A randomised trial of who prepares the SC injections (carer, nurse or pharmacist) was completed.
- In Singapore, a colour-coded pre-prepared 'Comfort Care Kit' is in use, (20) with oral and non-oral as-needed medication for caregiver administration. A telephone survey of 49 family carers showed that 67% used the kit, all family members found it easy, and 98% found it effective for symptom management. All except one patient died at home.
- In Canberra, the provision of an Emergency Medical Kit was largely viewed as an effective strategy in giving timely symptom control and preventing in-patient admissions. (21)

C. There is growing UK evidence on carer-role for patients in the last months/year of life, but there is still a paucity of studies focussing on last days of life (as reiterated by the Neuberger Review into the Liverpool Care Pathway (22))

- The evidence that is beginning to accumulate mostly focuses on competent patients within the last year of life. UK/Australian research includes 'Unpacking the home', (23) (24), The Cancer Carers Medication Management work (25), the SMARTE study (26), and IMPACCT. (27)
- Our project, in contrast, focusses on the last few days of life, with very different implications and issues for carer-administration.

Community receptivity

We contend that the UK is likely to be ready for testing this extended lay carer role.

- Primary care teams and families are used to similar practices in other areas of medicine (insulin for diabetes, intravenous antibiotics for children with cystic fibrosis).
- The Palliative and End of Life Care Priority Setting Partnership report incorporated the views of 1,403 people across the UK and placed great emphasis on empowerment of family carers and symptom management during the last days of life. (13)
- The 'Ambitions for Palliative and End of Life Care: a framework for local action' was published in Sept 2015. (28) It was jointly developed and published by the National Partnership for Palliative and End of

Life Care (27 national organisations) and has widespread support, especially as the Partnership included the Patients' Association and charities with large 'PPI' groups. They identified 8 foundations for the 6 ambitions, one of these foundations relates to "Involving, supporting and caring for those important to the dying person", acknowledging that their importance in the caring team. Each ambition has a set of building blocks – the one on "practical support" in ambition 6 is particularly applicable to CARiAD. There has been strong positive reception to the document, and many localities are using the framework to consider their local strategies. Specifically, its message about shared ownership and responsibility is particularly pertinent.

- In the UK, we have identified at least four geographically distinct sites where this practice is part of usual care; and two additional sites have already expressed interest to join a future main trial.

Pressure on health and care services in the UK:

We have engaged with HCPs in all three sites; they have been universally positive; this could make their patients more comfortable and their jobs more do-able. In the longer term, this innovation could relieve some pressure on Emergency Departments by reducing inappropriate emergency (crisis) admissions due to uncontrolled symptoms. (16) (17)
In due course, pressure on DN time could be relieved as extra visits (in addition to the daily check) to administer as-needed medication would reduce, contributing to sustainability of services. For the success of the CARiAD feasibility study we have carefully costed the additional DN and Research Nurse time necessary for successful recruitment and training.

Choice of design

Our team is aware of the challenges associated with research in the last days to weeks of life in general, including recruitment and ethical considerations. Whilst we recognise the benefits of conducting an internal pilot trial with progression rules to a full trial we feel that an external pilot and feasibility study is more appropriate. Regarding recruitment, an external pilot trial requires 3 sites recruiting 50 patients. A full trial would require 30 sites recruiting 520 patients. Although our 3 sites are confident about recruitment, and a number of other areas have already expressed interest in participating in a future trial, we cannot disregard the impact of the other complex factors affecting a broader roll-out.

These specific additional considerations resulted in the decision to propose a stand-alone (external) pilot trial:

- The current UK context (post-Shipman, post-Liverpool Care Pathway and with the ongoing euthanasia public debate): this calls for careful attention to its impact on consent mechanisms and attitudes of carers, patients and clinicians to this innovation
- Lack of clear UK-wide guidance on carer-administration of as-needed SC medication to dying home-based patients: The practice is legal but current guidance is not detailed nor specific enough for wide adoption. (see 'Appendix 1 - Legal framework')
- Lack of a clear and widely accepted training package for lay carers, adapted for the UK context
- Uncertainty about the primary outcome measure for a definitive trial

These are unpredictable barriers until we begin to introduce the re-worked Australian manualised intervention, and test the trial processes. If the intervention is proven feasible and acceptable, we anticipate a phase of

ensuring new guidance is developed and put in place at national level in UK health systems to enable the practice prior to rolling out a full trial quickly.

We will demonstrate a clear path towards a definitive randomised controlled trial as per MRC Framework for the evaluation of complex interventions principles; further informed by the MORECare guidance developed for palliative care research. (29) (30)

b. Phase 1 work

Expert Stakeholder Workshops

To inform the development of the intervention and specific processes at each site, three expert stakeholder workshops were conducted, one in each recruitment site. Half-day face-to face workshops, based on the successful model used in the ELCID trial, (31) were convened. Each workshop had 10-15 participants representing patients, carers, general practitioners (GPs), DNs, pharmacists and specialist palliative care (SPC) clinicians. Two research team members facilitated, setting the context and background to the proposed intervention. Notes were kept which allowed a report of proceedings to be generated.

Participants discussed and reached consensus on trial procedures:

- Identification (including risk assessment) of and approach to participants
- Consent
- Prescription, supply and storage of drugs
- Delivery of the intervention
- Monitoring and accountability
- Outcome measures collection
- Post-bereavement interviews
- Ethical considerations

The outcomes of these decisions are reflected in the trial procedures and the trial-specific materials:
For HCPs – prescribing advice for HCPs (relating to patients and carer in the intervention arm), competency checklist, risk assessment
For carers – Carer Diary, carer information booklet 'Subcutaneous medication for breakthrough symptoms in the last days of life: a Guide for carers', step-by-step guides

3. TRIAL OBJECTIVES AND DESIGN

a. Research question

Research Question: Is carer-administration of as-needed SC medication for breakthrough symptoms in homebased dying patients feasible and acceptable in the UK?

P = Patients in the last days of life who are becoming unable to take their usual oral as –needed medication for breakthrough symptoms, being cared for at home, and their carers

I = Carer-administration of as-needed SC medication for common breakthrough symptoms such as pain, restlessness/agitation, nausea/vomiting, and noisy breathing/rattle, supported by tailored education

C = Usual care (HCP-administration of as-needed SC medication)

O = Main outcomes of interest: Feasibility and acceptability, recruitment, attrition, contamination

b. Aims and objectives

To inform the design of a phase 3 trial, we aim:

A. To tailor a successful Australian intervention as a standardised, manualised intervention for UK carer-administration of as-needed SC medication for breakthrough symptoms in homebased dying patients.

B. To establish the feasibility of this standardised manualised package and carer role extension by assessing acceptability, ability to recruit, attrition rates, suitability to UK context. This will be done by conducting an external randomised pilot trial with embedded qualitative component.

C. To identify attributes pertinent to carers' preferences for HCP versus own administration of as-needed SC medications for home-based dying patients (as part of qualitative component) and to establish the feasibility of completion of the Carer Experience Scale.(assessed within the pilot trial)

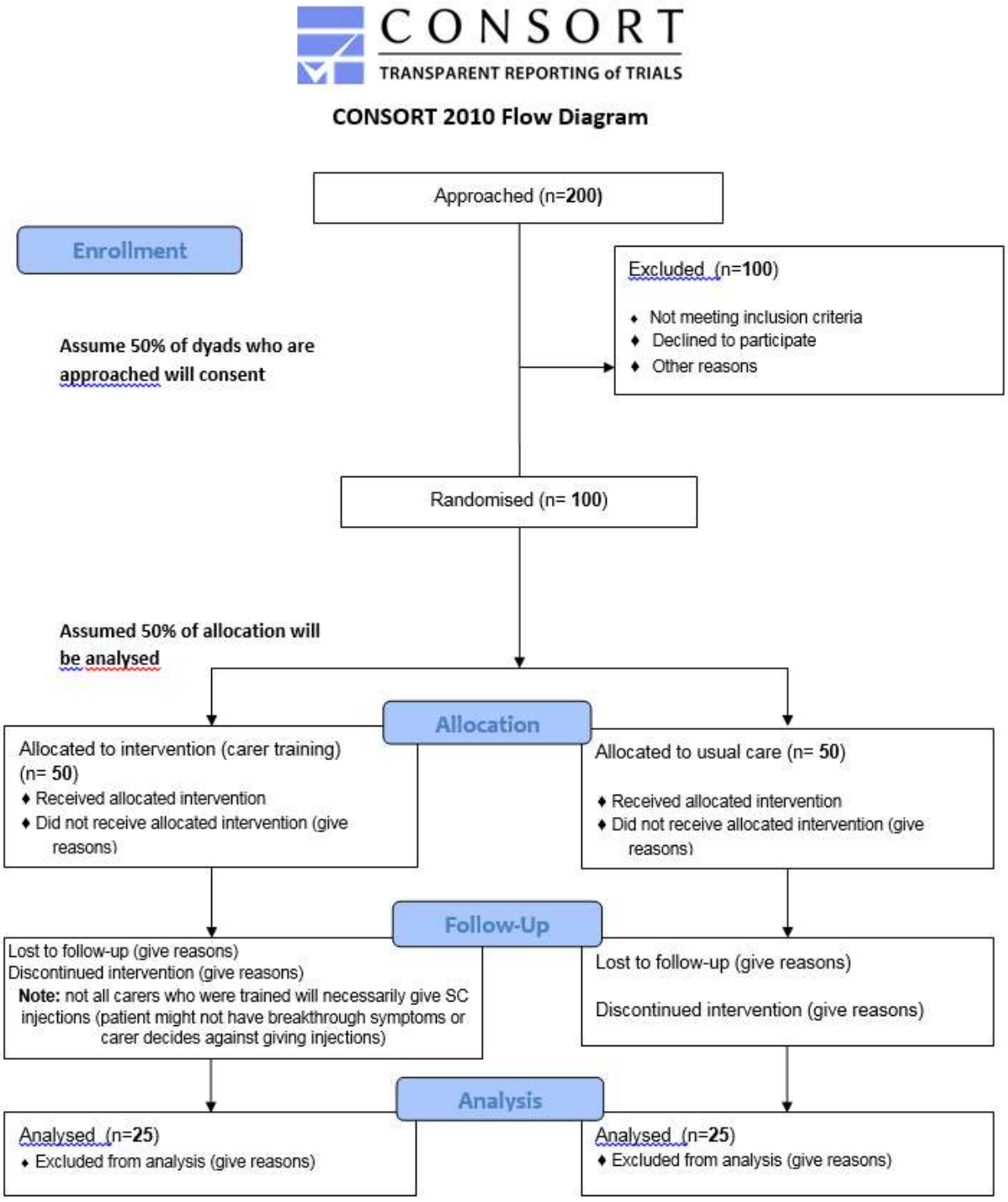
c. Trial design summary

Feasibility study and external randomised pilot trial of carer-administered as-needed subcutaneous (SC) medication for common breakthrough symptoms in home-based dying patients, versus usual care, with embedded qualitative component.

This will form the first phase of a future substantive trial if criteria are met. The pilot trial is a rehearsal of all the procedures and logistics that could be undertaken in a future main trial. The MHRA have advised that this pilot randomised trial is not a CTIMP. (see 'Appendix 2 – Clinical Trial Authorisation requirements')

Pilot randomised trial	
Trial setting	Community setting without 24/7 paid care
Trial Participants	Patient/lay carer dyads: Patients in the last days of life who become unable to take their usual oral as-needed medication for breakthrough symptoms, being cared for at home, and their carers
Technology	Carer-administered as-needed SC medication for breakthrough pain, agitation/restlessness, nausea/vomiting, or noisy breathing supported by a tailored education programme
Planned Sample Size	25 per arm (approach 200 potential participants to achieve 100 randomised participants, with 50 completers)
Care Pathways	Current (usual): Carers call a HCP who will travel to the home, assess, and give SC medication Planned intervention: Carers trained to assess need for, and give SC medication, and assess symptom resolution
Treatment duration	For the patients, until death
Follow up duration	For carers, up to 4 months post-bereavement
Planned Trial Period	1 November 2016 to 1 May 2019
Outcome measures	Pilot trial: Feasibility acceptability recruitment rate, attrition, contamination
	Potential main outcomes for a future definitive trial: Symptom burden, carer quality of life (Family MSAS-GDI, QOLLTI-F) Also: Time to symptom relief, number of episodes resolved in 30 minutes, safety, Carer Experience Scale, healthcare utilisation. Attribute selection for a future discrete choice experiment
Analysis	Feasibility metrics, adherence outcomes Preliminary analysis of intervention outcomes Point and 95% confidence interval estimates will be calculated and used to estimate standard deviations and effect sizes to further inform the sample size calculation for a definitive study
Embedded Qualitative study	Interviews at 2-4m post-bereavement to explore attitudes and experiences of giving SC medication, experience of trial processes (recruitment, consent, randomisation, training, medication management, outcomes – choice, timing and recording) Purposive sample of 6-10 carers (trained to give SC medication), 6-10 control group, 6-10 declined to participate, and prescribers 10 per group: GPs, DNs, palliative care clinicians. Questions regarding attributes for a discrete choice experiment in a future main trial will be included in these interviews Analysis – Carers: Interpretative Phenomenological Analysis for deeper, experiential inductive analysis. HCP analysis: Process driven deductive approach using Framework Analysis

d. Trial flowchart



4. SELECTION AND WITHDRAWAL OF SUBJECTS

a. Trial setting/context

Community setting without 24/7 paid care.
Gloucestershire, North Wales and Cardiff and Vale community settings where patients are likely to die at home in accordance with their wishes.
Pilot study sites have been chosen as they are representative of the range of sites for a future substantive study in order to best estimate typical recruitment rates. Two further areas have also indicated an interest in participation, but the external pilot numbers and generalisability are satisfied by our existing three areas.

b. Eligibility criteria

Inclusion criteria

Dyads of

- A patient in the last weeks of life
  - Who is likely to lose the oral route for medication, and
  - Who has expressed a preference to die at home
  - Is 18 years old
- And their family carer
  - Who is/are over 18, and
  - Is willing to have this extended role, and
  - Is willing to have SC injection training.

Due to the nature of the study we expect that there will be a high level of attrition. We therefore aim to approach 200 dyads (66-67 in each area) over a period of 12 months to obtain 50 completers at follow-up.
Our target population are patient/carer dyads, where the patient is in the last weeks of life and has expressed a preference to die at home, and have a relative or unpaid carer over 18, who is willing to have SC injection training. There is an assumption that the relative or carer will spend a significant amount of time with the patient, and whilst international experience finds that one lay person generally takes a lead role in this practice, where there is more than one carer we will ask the patient to identify which carer they would like to be included in the study.

Exclusion criteria

Patients who have only paid/formal care will be excluded. Patients or lay carers who are not willing to entertain the concept of lay carer administering SC medication, or where there is a known history of substance abuse, will not be approached. Patients with previously known adverse reactions to the 'usual' as-needed medications will also be excluded. In cases where HCPs judge that the risk assessment criteria are not met, dyads will not be approached for consent to participate.

See 'Appendix 3 – Outcome measures' for the Risk assessment.

c. Recruitment

Patient identification

Patient / carer dyads will be identified in a number of ways through the hospice, SPC service, or DN team identifying dyads suitable for the trial. When a patient is perceived by the HCP team to be in the last weeks of life and they have expressed a wish to be cared for and die at home, they will be screened for approach.

Screening

Eligible dyads must have satisfied the risk assessment criteria. A risk assessment screening tool has been refined for CARiAD, based on existing self-medication tools. (32) (See 'Appendix 3 – Outcome measures') Risk assessment will take into account several factors, including the carers' mental state, vision and physical condition. It will take into account the dyad's social circumstances as well as both parties' attitude to and knowledge about medicines as well as any relational issues including concerns about burden. The risk assessment will be conducted by the healthcare team involved in the patient's care. If a dyad does not satisfy the risk assessment criteria, they will be deemed ineligible to be approached.

We aim to have 100 dyads willing to consent to participate (33-34 in each area).

d. Informed consent

Advance consent will be sought from both the patient and their lay carer at a time point judged to be suitable for discussion by the attending HCP, when the patient is in the dying phase, e.g. a number of weeks anticipated life. This gives the patient and carer a chance to gain individual knowledge about the nature of the research, ask questions, make their feelings clear on trial participation and inform the subsequent discussion with the Personal Consultee.

The patient will be approached with written material (Participant Information Sheet and Consent form as approved by the REC and in compliance with GCP, local regulatory requirements and legal requirements). Initial patient approach will be done separately from the carer, unless otherwise requested by the patient and if the attending HCP deems this appropriate i.e. there is no risk of patient-carer coercion. Where more than one carer may be available, the patient will be asked at initial approach to identify who they would like to be included in the study as their carer. As the project involves sites in Wales, to comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms will be translated into Welsh and offered bilingually. Dyads will be given as much time as they need to consider the information sheets and discuss with family, friends or the healthcare team until they decide whether to take part.

For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision.
- be able to make a free choice

- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

The right of a participant to refuse participation without giving reasons will be respected. Participants remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. This will be made clear to all potential participants at consent and throughout their time in the trial.

Even if the patient has consented, once they lose capacity, a Personal Consultee (as required by the MCA) will need to give their assent. As the risk assessment will exclude dyads where there are concerns about relational issues between patient and carer, the carer can act as Personal Consultee.

In the circumstance when there is no additional family member or close friend to act as the Personal Consultee, we will seek to appoint a Nominated Consultee (e.g. a member of hospice staff not associated with the research) who may be able to act for all patients in this circumstance in the trial.

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki.

e. Randomisation scheme

Method of implementing the allocation sequence

Consented dyads will first complete baseline information before being individually randomised. The randomisation will be performed by dynamic allocation to protect against subversion while ensuring that the trial maintains good balance to the allocation ratio of 1:1 both within each stratification variable (recruitment centre and cancer/non-cancer) and across the trial. (33)

Randomisation will be performed by the researcher who has taken informed consent, and will be achieved by secure web access to the remote randomisation centre at NWORTH, Bangor University. This system will be set up, maintained and monitored independently of the trial statistician or other trial staff. The randomisation system provides an opportunity to check the entry of the details before randomisation is performed. Dependent on whether the researcher is required to be blinded or not the system will either confirm a successful randomisation or provide the result on screen. Confirmation emails to the pre-defined emails will be sent notifying the relevant people of the randomisation result.

A detailed randomisation specification will be drawn up prior to set up of the system that will detail the technical system requirements, this will be guided by NWORTHS SOPs.

f. Blinding

CARiAD is an open-label trial where true blinded outcome assessment is not feasible, and therefore it is important that outcomes are as robust as possible to the lack of blinding. Table 1 details the primary outcome contenders, the manner in which we will collect these independently and as 'blind' as possible on at least one or two occasions, the methods of assessment, strategies to reduce bias (by increasing subjectivity) and criteria for assessing feasibility as primary outcome measure for a future definitive trial. Outcome assessors will be trained and observed in their measurements to increase consistency.
Data analysis will occur blinded to treatment allocation. Unblinding of this analysis will occur at a management meeting with independent members present.

g. Withdrawal criteria

Participant withdrawal from the study will not affect their medical care, and this point will be emphasised in the patient information sheet and during the informed consent process.

Non-completion of the follow-up questionnaires will not constitute formal withdrawal from the trial, and unless the participant requests withdrawal of their data completely, it may be used to impute values for the analysis.

The risk assessment will be reviewed at intervals and if the criteria are not met the dyad will be withdrawn from the trial.

h. Expected Duration of Feasibility Study

12 month recruitment period (October 2017 to September 2018)

5. FEASIBILITY STUDY PROCEDURES

a. Feasibility study interventions

Health technologies being assessed

The technology is the extended role of lay carers to administer as-needed SC injections for common symptoms like pain, nausea, and restlessness to a person dying at home. Lay carers will be trained in this practice, and their training will be supported by a manualised training package and programme based on the Australian package 'Caring Safely at Home'. Note: it is already usual practice to ensure provision of as-needed medicines for breakthrough symptoms in the patient's home, for administration by the attending clinician. The difference in technology is that carers will be trained to administer these drugs (rather than and in addition to clinician-administration).

Content and timing of training

Lay carers will receive training on

- Common symptoms that may occur in the last days of life, and how to assess if their loved one needs medication for a particular symptom
- How to prepare (draw up) medication and dispose of sharps (glass ampoules and drawing up needles)
- How to administer SC medication by needle-less technique (utilising a 'butterfly' SC catheter)
- How to assess the effect of the medication
- Support available, including primary care team as well as dedicated 24/7 SPC support

If a symptom occurs for which medication is deemed necessary (either as expressed by the patient if able, or by the carer's assessment), the carer can use the training outlined above to administer the appropriate medication.

The 'Caring Safely at Home' package will be adapted for UK use. For more detail on the education programme and materials, see 'Appendix 4 – Caring Safely at Home materials'.

We know that lay carers gain their competency and confidence over time which is an important consideration for any implementation. (34) We will anticipate debate within the palliative care community around the best time to introduce the topic to patients and their carers, as well as when to commence education to lay carers. There is initial research in the area which informed the Supporting Carers at Home trial timings through qualitative interviews.

Medication regimens

Guidelines for anticipatory prescribing for last days of life care are firmly in place across the UK. It covers common symptoms in the dying phase, specifically pain, nausea and/or vomiting, restlessness/agitation and noisy breathing/rattle. CARiAD recruitment sites will be advised to follow usual practice with regards to what medication to prescribe. For example, in Wales, as-needed SC medication prescribing advice includes:

- For pain: morphine or diamorphine at one sixth of the 24 hour dose, or if a patient is not on background strong opioids, a starting dose of diamorphine 2.5-5 mg or morphine 5 mg.
- For nausea and/or vomiting: Cyclizine 50 mg (maximum dose in 24 hours = 150 mg) or Levomepromazine 6.25 mg
- For restlessness/agitation: Midazolam 2.5-5 mg

- For noisy breathing/rattle: Hyoscine hydrobromide 400 mcg or Glycopyrronium 200 mcg

Prescribers with patients in the intervention arm will be provided with information they should consider when prescribing medication for carer administration e.g. no dose ranges, no remote dose changes.

Care Pathways

The usual care arm has an unchanged care pathway for dealing with breakthrough symptoms at home for a dying patient. Once a patient has started to lose their oral route, they are attended by DNs, with support from hospice nurses or doctors with helplines available. The GP and other primary care providers (including OOH services) will be involved as necessary (e.g. prescribing, home visits), and usually the DNs set up a syringe driver to deliver 24 hr SC medications through a butterfly needle. Good anticipatory care ensures SC meds are available for breakthrough symptoms, and carers would normally call the DN who will travel to the home, assess, and give SC medication.

'Usual routes' for support in each recruitment area are different. For some areas there is direct access to a 24/7 SPC advice line for HCPs and carers (in addition to the option to call on their primary care team within or out-of-hours). In other areas the first tier of support for the carer will be via their primary care team, with the HCPs having the option of calling for advice from SPC clinicians (as a second tier).

For each recruitment area, the following will be clearly set out in standard operating procedures:

- clinical support for dyads, and for their primary care HCPs, towards SPC advice (in a clear pathway diagram).
- research support, including when, how and in what circumstances the research team should be accessed as part of this 'pathway' of support.

In the Intervention arm, carers will be trained to have the option to administer as –needed SC medication:

- The carers of dyads randomised to the intervention arm, will receive training on:
    - Common symptoms that may occur in the last days of life, and how to assess if their loved one needs medication for a particular symptom
    - How to prepare (draw up) medication and dispose of sharps (glass ampoules and drawing up needles)
    - How to administer SC medication by needle-less technique (utilising a SC catheter)
    - How to assess the effect of the medication
    - Support available, including primary care team and 24/7 SPC support - If a symptom occurs for which medication is deemed necessary (either as expressed by the patient if able, or by the carer's assessment), the carer can use the training outlined above to administer the appropriate medication.
    - Carers will be made aware that they should not administer any subcutaneous medications to the patient if they are admitted to any inpatient unit (including hospital or hospice).

- It will be made very clear that the carer is under no obligation to give as-needed SC medication. If the carer feels they want the support of a HCP, they can trigger this support via the usual routes in their

area (which might include DN team, GP, GP/DN out-of-hours, Hospice at Home team, hospice advice line).

The planned care pathway for the 'usual care' arm is the same as the current standard care pathway. The intervention arm differs from usual care; with the carer giving SC injections for breakthrough symptoms.
In both arms, these aspects of the current care pathway will remain in place:

- Patients will be visited daily by a member of the healthcare team, usually a district nurse.
- As per local guidelines for anticipatory care of common symptoms in the last days of life, there will be a supply of drugs in the patient's home, combined with the apparatus needed to administer them. (35) (36)

Trial processes will include the measurement of outcomes in both usual care and intervention arms, as follows:

- Carers will keep a diary (adapted for UK from the Australian training package) and record:
  - the date/time when one of the dyad felt the patient needed medication for a symptom
  - symptom score (Numeric rating scale 0–10, 0 no symptom, 10 = worst possible symptom)
  - the date/time when the medication was administered (as well as details of the medication and dose)
  - symptom score and whether/when the patient (if able) or carer feels the symptom has been significantly relieved, approximately 30 minutes after medication administration
  - any relevant notes
  - admission to hospice or hospital for crisis care
- two to four months post-bereavement, the carer will be asked to complete the MSAS-GDI, a measure of the patient's symptom distress in the last 7 days of life

The CARiAD study is focussing on the management of breakthrough symptoms requiring the use of as-needed SC medication. This is in addition to any measures already put in place to manage background symptoms (for example, a patient might already be receiving one or more medications via continuous SC infusion). It is understood that, even if background symptoms are well-controlled, patients may still experience episodic symptoms, 'breaking through' the background medication, and hence referred to as breakthrough symptoms. If a patient needs several doses of as-needed medication for a particular symptom in a 24 hour period, it is usual practice to either start (or increase the dose if already given) a continuous infusion of a medication, to reduce the likelihood of further as-needed doses.

HCP training requirements

In order for the DNs to train family carers, they will receive detailed information on the standardised manualised education package (adapted from the Australian work, see 'Appendix 4 – Caring Safely at Home materials'). Training will include symptom management and will be delivered with the support of SPC clinicians. The legal framework and guidelines for medication handling and administration in a community setting will be considered. They will also receive training on trial-specific materials and processes.

b. Schedule of procedures

	Time points

Procedures		Screening	Baseline	Study period (last days of life)	Post-bereavement
Eligibility assessment		As per dyad inclusion/exclusion criteria			
Informed consent		Advance consent from dyad	Check consent	Check consent (Personal Consultee assent might be required when patient lose capacity)	
Demographics			CRF		
Medical history			CRF		
Concomitant medications			CRF	CRF	
Randomisation					
Assessment: Symptom control	Symptom scores			Tool: **Carer Diary** ▪ Completed by: carer ▪ When: at every occurrence of symptom if patient able to score	
	Overall symptom burden				Tool: **Family MSAS-GDI** ▪ Completed by: Carer and HCP ▪ When: at initial (immediate) post-bereavement visit Tool: **Qualitative interviewing** ▪ Completed by: Carer ▪ When: Post-bereavement
	Time to symptom relief			Measure: **Episodes resolved in 30 minutes** ▪ Completed by: carer ▪ When: 30 minutes after drug administration Measure: **Time when control achieved or symptom reduced to an acceptable level** ▪ Completed by: carer ▪ When: after drug administration	Tool: **Qualitative interviewing** ▪ Completed by: Carer ▪ When: Post-bereavement
Assessment: Safety	Risk assessment	Tool: **Adapted tool based on Fullers self-medication risk assessment screening tool** ▪ Completed by: HCP ▪ When: Prior to dyads being approached to take part in the study (in order to satisfy eligibility criteria			
	Competency Checklist		Tool: **Competency Checklist** ▪ Completed by: HCP ▪ When: on completion of training and if deemed necessary afterwards	Tool: **Competency Checklist** ▪ Completed by: HCP ▪ When: on completion of training and if deemed necessary afterwards	

		Time points			
Procedures		**Screening**	**Baseline**	**Study period (last days of life)**	**Post-bereavement**
	Significant Event Reporting			Including appropriateness of administration, proportionality, side effects, drug accountability, carer events	
	Evaluation of training package				Tool: **Qualitative interviewing** ▪ Completed by: Carer and HCP ▪ When: Post-bereavement
Assessment: Impact on carer	Self-efficacy		Tool: **QOLLTI-F** ▪ Completed by: Carer ▪ When: At baseline before randomisation	Tool: **QOLLTI-F** ▪ Completed by: Carer ▪ When: every 48 hours from when the patient first needs as-needed SC medication	Tool: **Qualitative interviewing** ▪ Completed by: Carer ▪ When: Post-bereavement
	Confidence			Tool: **Carer Diary** ▪ Completed by: carer ▪ When: after giving every injection	
Assessment: Health Economic outcomes	Impact on carers		Tool: **Carer Experience Scale** ▪ Completed by: Carer ▪ When: Baseline		Tool: **Carer Experience Scale** ▪ Completed by: Carer ▪ When: Post-bereavement
	DCE attribute selection				Tool: **Qualitative interviewing** ▪ Completed by: Carer ▪ When: Post-bereavement

c. Randomised Feasibility Study Outcome measures/endpoints

The main outcomes of interest will be those appropriate to an external pilot trial, including feasibility, acceptability, recruitment rates, attrition and selection of the most appropriate outcomes measures. Outcomes will be measured for patients, their lay carers, health care professionals, and system barriers. These measurements will be made at baseline, on a daily basis for symptom control and lay carer confidence, at initial bereavement visits, and at 6-8 weeks post bereavement for a sub-sample.

Recruitment measurements:

- The number of eligible patients who fulfilled the inclusion criteria and were willing to be randomised will be expressed as a percentage of the numbers screened.
- The number who withdraw after baseline assessment and randomisation.
- The number who complete the various outcome measurements at baseline and at later time points.
- The researchers who administer the outcome measures will record the reasons for any non-completion.

Patient measurements

Baseline information including demographic information, medical history, level of capacity at entry, preferred place of care, and current management. A daily Carer Diary during the study related to the presence and treatment of breakthrough symptoms (for use in both study arms). Data points to include initial time breakthrough symptom triggered perceived need for an additional SC dose, whether noted by patient or lay carer, date, time, medication, dose, reason for medication (pain, nausea restlessness, other), symptom score before and 30 minutes after medication administration, when symptom control was achieved/reduction of symptom to acceptable level. Actual place of death, and hospital or hospice admissions during last illness.

Carer measurements

Demographic information at baseline, confidence (in administering injection) and competence at intervals after training, QOLLTI-F every 48 hours, whether HCP support was sought, Carer Experience Scale at baseline and post-bereavement , Family MSAS-GDI at immediate bereavement visit, and qualitative interviews for a sub-sample at 2-4 months post-bereavement.

The Case Report Form (CRF) will capture demographic information of the patient and carer, and relevant patient-specific information (diagnosis, concurrent medical history, current management including regular medication, mental capacity, preferred place of care, current place of care, and place of death). Confidence in administering SC medications will be recorded for carers in the intervention arm. The healthcare team will be characterised, recording the attending team structure, primary prescriber and primary trainer (of carer).

Health care professional measurements

Baseline measurements of attending team structure, primary prescriber, who trained the attending clinician (assumed to be a DN in most cases), and HCP evaluation of the training package.

Safety

The CARiAD project contains a number of safety outcome measures at different stages of the clinical journey taken by the patient, carer and HCPs as the safety issues relate to all involved.

Safety outcome measures include:

- Risk assessment (see 'Appendix 3 – Outcome measures')
- Competency checklist
- Significant Event reporting

Significant event reporting will include the following:

- Appropriateness of administration: is administration accompanied by evidence of need?
- Proportionality: has the correct dose been administered?
- Side effects: both anticipated and not anticipated
- Drug accountability: do stocks tally?
- Carer events e.g. distress; needle stick injury; accidental or purposeful self-administration

All events will be captured via SAE reporting forms. As this is a study in patients who are terminally ill, it is to be expected that death will be a frequent outcome. It will be recorded and reported to the sponsor, but will not

be considered a serious unexpected adverse event if, in the opinion of the Principal Investigator, it was a natural conclusion to a patient's terminal illness. Due to the nature of the study, events of death will not require immediate reporting to the Ethics Committee.

d. Exploratory endpoints/outcomes for a future definitive trial

The most likely candidates for primary outcome measures for a future definitive trial are:

- **Family MSAS-GDI**

A measure of overall symptom burden/distress in the last seven days of life. (12) (37) (38) (39),

- **QOLLTI-F**

A measure of quality of life of carers looking after someone with a life-threatening illness, incorporating elements of control and self-efficacy. QOLLTI-F will be in addition to other measures, specifically, measuring carer confidence using a five point Likert scale (where the carer is asked after administration of every as-needed SC injection to rate their level of confidence in administering this injection, 1=not at all confident, 5=very confident), and probing carer experience during the qualitative interviews. We will integrate the qualitative results with the quantitative measure.

We will use the consensus phase (Expert Consensus Group) and the qualitative component to ensure we are using the most acceptable carer quality of life/self-efficacy and symptom/distress assessment and that they are adequately capturing the carer and patient experience. For all of the outcomes the other issues of tool completion, perceived difficulty and perceived usefulness will inform feasibility for a larger trial.

Rationale for the choice of Family MSAS-GDI:

- The Memorial Symptom Assessment Scale (MSAS) (32 items) is a valid and reliable patient self-report instrument. (12) The MSAS-GDI has demonstrated reliability and validity measuring global symptom distress from the patient perspective. Although the scale was designed to produce one single score, the individual items can also be used as single item indicators of burdensome symptoms at the end of life identifying which symptoms are getting better or worse over time in different patient populations. (37)
- Hickman et al (2001) showed that the MSAS-GDI is amenable to modification for use in research with recently bereaved family respondents whose family members died from a wide range of causes. (37) Items were modified so that the questions focused on the symptoms experienced by decedents in the last week of life as observed by family respondents. The Family MSAS-GDI, has good face validity for use in understanding symptoms experienced by patients in the last week of life, regardless of cause of death or role in relation to the patient (carer or HCP) . (39)
- In the Hickman et al study (2001) of 103 family members, mean Family MSAS-GDI score was 1.14 (SD = 0.87) with a range of 0 to 3.73. The scale demonstrated good internal consistency ($\alpha = 0.82$). The average item-total correlation was $r = 0.49$ and the average inter-item correlation was $r = 0.30$, suggesting items were moderately correlated with the overall total scale and with each other. They concluded the Family MSAS-GDI could prove to be a useful tool in assessing and tracking global symptom distress in dying patients. (37)
- Lobchuk's (2003) work corroborates these findings, showing good to excellent intra-class correlations (ICC) with patients' ordinal ratings to support the concurrent validity and utility of the MSAS-GDI subscales in family carer populations who care for cancer patients in the home setting. (38)

Rationale for the choice of QOLLTI-F:

- It has established psychometric properties (reported validity and reliability, demonstrated responsiveness, no floor and ceiling effects), is relatively brief (16 items) and can be administered every 2 days (rather than daily, reducing the risk of overburdening carers).
- It is broadly aimed at carer quality of life, and incorporates issues of control (reported as paramount by carers) and self-efficacy (conceptualised as "a person's belief about her or his ability to organize and execute courses of action to manage given situations").

Criteria for assessing feasibility as primary outcome measure:

All outcome measures will be assessed on the same criteria for consistency

Applicability

- Assessed by an independent expert panel based on feedback from participants (HCPs and carers).
- Each measure will be assessed by the panel with regard to its relevance and applicability to the population. This can be done based on the outcomes of the pilot data collection phase.
- The panel will recommend a 'Accept' or 'Not accept' status for each outcome based on the criteria below, their expert opinions and taking into account the RATIONALE statements on outcome measures (40) and assessment of bias risks in ultimate reporting. (41)

Acceptability

- Assessed by participants and HCPs during the qualitative aspects of the feedback interviews.

Level of completeness

- Assessed by the frequency of missing data during the data collection phase. This would require potential primary outcome measures to have greater than 70% completeness.
- An assessment will also be made of the reasons for missingness to establish whether anything systematic within the design could be adjusted to mitigate for the missingness.

Once the feasibility of the outcomes is established, the design of the definitive trial will consider whether a single or combined primary outcome of interest is appropriate.

The potential suitability of the secondary outcomes will be considered as detailed below.

'Time to symptom relief'
This measure will be collected given the importance of this outcome to carers and patients. It does, however, present significant inherent challenges with potential bias, and will not contend as a primary outcome measure for a future definitive trial unless methodological concerns are resolved. The specific methodological concern is that it will be hard to demonstrate that the measurement of this outcome will be done in comparable ways in the two arms of the trials. We acknowledge that these problems arise because the individual measuring the outcome (the carer) cannot be blind to the study arm. The intervention arm will have lay carers deciding to dispense treatment, and this could systematically affect their judgement of this outcome.

Carer Experience Scale:
The Carer Experience Scale (CES) is an index measure of the caring experience, focusing on six domains: activities outside caring, support from family and friends, assistance from the government and other organizations, fulfilment from caring, control over caring and getting on with the care recipient. The construct validity of the CES instrument has been demonstrated in a heterogeneous group of 730 carers in the UK, (42) and specifically in the context of palliative care. (43) The CES benefits from having preference-based index values, based on 162 unpaid carers of older people from 5 geographical locations in the UK, (44) that allows for calculation of utility for use in economic evaluations.

Table 1: Qualities of potential future outcome measures under investigation in CARIAD

Outcome measure	1. Description	2. Method(s) of assessment
Family MSAS-GDI For the tool, see Appendix 3	▪ The Family MSAS-GDI has established validity and reliability when used to provide a measure of overall symptom burden/distress in the last seven days of life. It has in-built averages: It is the **average of the frequency** of 4 prevalent psychological symptoms (feeling sad, worrying, feeling irritable, and feeling nervous) and the **average of the distress** associated with 6 prevalent physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth) in the last seven days of life. ▪ This measure is less likely to differ systematically between the two arms as it covers a wider range of experiences, and a longer time range than 'time to symptom relief' per episode. ▪ It is designed for proxy completion by carers and HCPs. Completion by HCPs will be a composite measure based on clinical parameters (as derived from daily clinical assessment) and carer (also unblinded) reports of symptoms as no HCP can be in attendance 24/7. ▪ It can be administered either face-2-face or via the telephone.	Family MSAS-GDI collected after the patient's death ▪ Carer proxy views will be collected by an independent observer (thus blind to treatment allocation, e.g. research nurse). This is likely to take place face-2-face. ▪ Attending HCP proxy views will be collected by an independent observer (e.g. research nurse). ▪ These independent observers will be trained and observed themselves to ensure a consistent approach. In addition to completing Family MSAS-GDI after the patient had died, this measure could be collected daily. ▪ Though Family MSAS-GDI was designed for completion reflecting on the last seven days of life, the tool can easily (and in minor ways) be amended for administration on a daily basis. ▪ The Expert Consensus Group (comprising of carers and HCPs) will be asked to consider the balance of benefit and burden and to advise if this option is to be pursued. Options include: ▪ Carer proxy views can be collected by an independent observer (e.g. research nurse), via daily telephone call. ▪ Attending HCP proxy views can be recorded either by the HCP themselves following their daily visit, or an independent observer (e.g. research nurse). HCPs will be asked to take into account the report of the carer, but also triangulate it with their own clinical assessment of the patient and knowledge of contextual factors.
QOLLTI-F For the tool, see Appendix 3	▪ QOLLTI-F has established psychometric properties (reported validity and reliability, demonstrated responsiveness, no floor and ceiling effects), is relatively brief (16 items) and can be administered every 2 days (rather than daily, reducing the risk of overburdening carers). ▪ It is broadly aimed at carer quality of life, and incorporates issues of control (reported as paramount by carers) and self-efficacy (conceptualised as "a person's belief about her or his ability to organize and execute courses of action to manage given situations"). ▪ This measure is also less likely than 'time to symptom relief' to differ systematically between study arms.	▪ QOLLTI-F will be collected by an independent observer (research nurse). It is administered every 48 hours. ▪ The Expert Consensus Group will be asked to consider how best to collect this data, including if this should happen face-to-face or via the telephone.

Outcome measure	1. Description	2. Method(s) of assessment
Time to symptom relief	This measure will be calculated using data items from the Carer Diary. We will minimise bias by using strict definitions of episode timings: ▪ The start of an episode is defined as the point at which the patient has a breakthrough symptom which triggers perceived need for an SC injection, either as per the view of the patient or the carer. ▪ Symptoms are defined as 'resolved' (indicating the end of an episode) at the point that the patient (or the carer if the patient is unable to) feels the symptom is felt to be controlled or reduced to an acceptable level and where more additional SC medication is not needed. ▪ If a patient needs a further dose of SC medication for the same symptom within 2 hours of the first injection, the episode will be classed as 'not resolved'. As the onset of an episode as well as the judgement when it is resolved is subjective, fidelity can be interrogated using objective data. We will assess bias by interrogating: ▪ The percentage of 'resolved within 30 mins of injection' episodes between both groups (i.e. at that point the measure between the two groups shouldn't differ significantly as the injection has already been given) rather than from time of onset of the symptom. ▪ The number of repeat SC injections within 2 hours. ▪ The symptom score recorded in relation to 'resolution'. ▪ The time to symptom relief minus travel time by HCPs (i.e. not taking HCP travel time into account).	▪ The Carer Diary is designed for completion by the carer, and will be collected from the carer after the patient had died. ▪ Blinded assessment is not possible as symptoms occur at random times and symptom scores are assessed when symptoms occur rather than at fixed time points, and no assessor (HCP or research nurse) can be in attendance 24/7. (Even if someone, e.g. another family carer/member, were able to be there at all times, they will not be blinded as treatment allocation will be obvious - either the carer is administering SC medication or not). We have considered other strategies: ▪ Measuring symptom scores at regular intervals e.g. every 30 minutes for 2 hours. The Expert Consensus Group will be asked to consider the balance of benefit and burden and to advise if this option is to be pursued. ▪ To compare the number of episodes of complete resolution not just between the two groups in the study, but also in a small cohort of patients in other 'immediate access to SC injection' settings such as a hospice or hospital. This could be done as a separate smaller study which is not part of this application.

e. Embedded qualitative study

The aim of the embedded qualitative component is to inform the definition of the design and assess the feasibility of a phase 3 trial of carer administered medication. The study will collect interview data from clinicians and carers to:

- Assess clinical willingness to randomise patients for a future full RCT.
- Understand the experience of randomisation between intervention and control, and to identify relevant patient-centred outcomes for a phase 3 trial, and to consider time points for assessment.

The qualitative study will further include interviews with non-consenters to the trial, as well as in-depth qualitative exploration of carer and HCP acceptability to carer-administered SC medication e.g. strong opioids, anti-emetics, sedatives. The study will use a phenomenological and pragmatic approach to understand the meaning that carer-administration of injectable strong opioids and other as-needed medication has for bereaved carers and HCPs and practicalities involved.

Sample

Face-to-face qualitative interviews across the three recruitment sites will be conducted with:

- 6-10 carers who have experience of supporting a home death. For carers, sampling criteria will include gender and rurality.
- 6-10 carers who have experience of supporting a patient receiving usual care.
- 30 prescribers. Ten each from GPs, administering health care professionals (e.g. DNs) and SPC clinicians. Sampling criteria will include years since qualification, experience of supporting home deaths and practice characteristics.
- 6-10 carers who declined to be randomised to the trial.

Consent

Carers declining to take part in the trial, will be approached upon declining and invited to participate in a different interview about the reasons why people choose not to participate in this trial. They will be given a separate information sheet for this.

Data gathering

Interview topic coverage was informed by PPI input, the systematic review, and the expert consensus workshop. Attitudes to and experiences of having administered the strong opioids including emotional, ethical and practical reflections will be explored, as will issues relating to trial recruitment and feasibility (supply and storage of medication, success of training and perceived competence of carer once trained, choice and recording of the primary outcome). Carers will be interviewed approximately 2-4 months post-bereavement (as suggested by usual clinical follow-up and current literature). (45) (46) (47) (1)

Interviews will be face-to-face at carers' homes or alternative preference; or possibly by telephone; lasting 30-60 minutes. The interviews with carers who declined to be randomised to the trial will be shorter, lasting 15-20 minutes. HCP interviews will last around 30 minutes. All interviews will be audio recorded, transcribed and the carer interviews will be managed using NVivo. Participants will be asked to consent to publication of their anonymised extracts.

Analysis

The analytic frameworks are selected to understand the meaning that carer-administration of injectable strong opioids and other as-needed medication has for bereaved carers and HCPs.

- Carer interviews will be analysed using Interpretative Phenomenological Analysis [IPA] to allow a deeper, inductive analysis of the data in the context of carers and patients' daily lives and values. (48) This methodology focusses on the subjective experience of participants, as interpreted by the researcher.
- HCP interviews will be analysed using Framework Analysis with a deductive approach. (49) Framework analysis is commonly used in healthcare and is more appropriate for examining the specific aims and objectives of an HCP. The data will be summarised thematically and displayed on a matrix linking to the original data.

f. Work-up towards future Discrete Choice Experiment (DCE)

We have identified the need to determine carers' preferences for HCP versus own administration of medication to patients, using a discrete choice experiment (DCE). The preferences of carers towards administering SC medications will have a bearing on their willingness to adopt this practice, and the effectiveness of carer-administered medicines. While the DCE will be conducted as part of a future main study, the preparatory work required to identify relevant attributes and levels will be done as part of the qualitative interviewing component of the feasibility study. This will be conducted in the second part of the interview and will take approximately 20 minutes. Attributes may feasibly include cost, time, perceived competency, confidence, and potential risks. The process of attribute development will be informed by best practice. (50)

The aim of the discrete choice experiment (as part of the main study) will be to ascertain carers' preferences for their administration of SC medications. As part of the embedded qualitative study, we aim to identify and rank factors that are important to carers in guiding their choice between HCP and own administration of SC medications.

Sample

Face-to-face qualitative interviews will be conducted (as described above) with each of the three carer groups. The use of interviews for the determination of DCE attributes enables a greater opportunity for in-depth exploration of particular issues and concepts than would otherwise be possible in focus groups (which are more common in DCE development). Individual interviews are also better suited to discussions concerning sensitive topics.

Analysis

Within the first five interviews in each group, carers will be presented with a range of attributes, identified by the research team as being likely to affect carers' choice for own versus HCP administration of SC medications. Interviewees will have an opportunity to add other factors of their own choosing to the list, and asked to identify and rank the top 10 by level of importance. Thereafter, we will use the interviews to pilot the presentation of the highest ranked attributes. The ordinal ranking across each group will be determined, and those ranked highest will be taken forward for DCE development. We have successfully implemented this

method in previous DCEs, (51) and it is consistent with the reductiveness approach of attribute development. (50)

We will also pilot the Carer Experience Scale as a means to estimate carer utility. (44) The index values derived from this scale offer a preference-based approach to incorporate the effects on carers in economic evaluation, focusing on care (rather than health)-related quality of life. (see 'Exploratory endpoints/outcomes for a future definitive trial: Carer Experience Scale')

6. ASSESSMENT OF SAFETY

a. Recording Adverse Events

Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ▪ results in death ▪ is life-threatening ▪ requires inpatient hospitalisation or prolongation of existing hospitalisation ▪ results in persistent or significant disability/incapacity ▪ consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

b. Procedures for Recording Adverse Events

All SAEs occurring from the time of start of the pilot trial treatment until the patient's death will be recorded on the SAE Reporting Form and faxed to the Sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached."

SAE reporting will include the following:

- Appropriateness of administration: is administration accompanied by evidence of need?
- Proportionality: has the correct dose been administered?
- Side effects: both anticipated and not anticipated
- Drug accountability: do stocks tally?
- Carer events e.g. distress; needle stick injury; accidental or purposeful self-administration

Responsibilities:

Principal Investigator (PI):

Checking for AEs

1. Using medical judgement in assigning seriousness, causality and expectedness
2. Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigators (CIs):

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning expectedness.
4. Review of specific SAEs in accordance with the trial risk assessment and protocol.

Sponsor:

1. Central data collection and verification of AEs and SAEs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the CIs for the ongoing assessment of the risk / benefit.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)).

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the Data Monitoring Committee (DMEC) regarding safety issues.

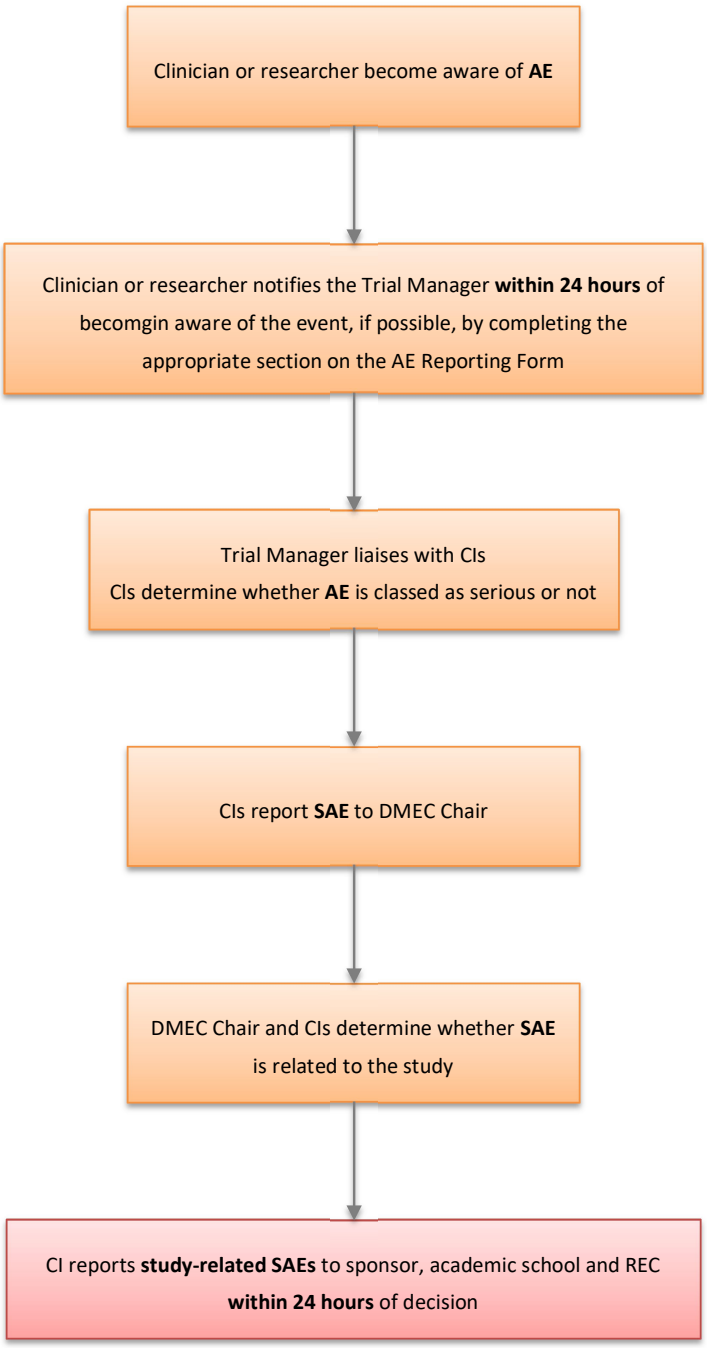
Data Monitoring Committee (DMEC):

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

Notification of deaths

As this is a study in patients who are terminally ill, it is to be expected that death will be a frequent outcome. It will be recorded and reported to the sponsor, but will not be considered a serious unexpected adverse event if, in the opinion of the Principal Investigator, it was a natural conclusion to a patient's terminal illness. Due to the nature of the study, events of death will not require immediate reporting to the Ethics Committee.

c. Safety Reporting Flow Chart



7. STATISTICS AND QUALITATIVE DATA ANALYSIS

a. Sample size calculation

Sample size for external pilot trial, and potential future main trial:
A fully justified sample size is not required; size is justified by estimating what a future full RCT will need. Assuming an important difference of 0.4 (SD=1) on the Family MSAS-GDI a sample of about 216 is required to achieve 90% power to detect a difference of this size with a significance level of 0.05 using a two sided test. Equivalently a sample of about 550 would be required to detect a difference of 0.5 points (SD=2) using the QOLLTI-F.
Using the larger of these estimates for the feasibility trial, we will assume about 9% of the main trial size, to give an 80% CI to exclude a clinically important difference, requires ~ 25 in each group. (52) Sim and Lewis recommend a sample of about 50-55 to ensure robust estimates of the variance. (53) Using estimates of dropouts we predict we need to approach 200 potential participants to achieve 100 randomised participants, with 50 completers. We will therefore need to approach 5.5 dyads per month from each of the 3 sites, and randomise 2.7 dyads per months from each of the 3 sites to meet our recruitment target.

Sampling for the pilot trial:
SPC nurses will train the DNs, who will in turn provide training to the lay carers. Our aim is to approach 200 dyads, assuming 100 might be randomised with 50 each in the intervention and usual care arms. Further, we assume attrition to half that number by the time we analyse, resulting in 25 dyads completing in each arm. So, assuming we will recruit equally between the three areas, we need to approach 66, randomise 33-34 and have 16-17 available per area for analysis.
As per the 2013 ONS data described earlier, we know that 8.58% of all deaths are home deaths due to neoplasms in those aged over 15. (54) Deaths due to neoplasms are seen as a useful proxy for expected deaths. Therefore, the 3 recruitment areas have the following numbers available per annum – North Wales 653, Gloucestershire 517, Cardiff and the Vale 349.

Table 2. Sample size calculations

Proposed Primary outcome measure	Outcome measure description	Estimate of a conservative effect	Sample needed	Rationale
Family MSAS-GDI	11 item scale rated 0-4 for each item. Score is given as the mean of the 11 items, giving an overall scale of 0-4.	Difference of 0.4 points (SD= 1.0)	216	Hickman 2001 (37) indicated a SD of 0.87 this reduces the sample size to 164
QOLLTI-F	16 item scale rated 0-10 for each item. Score is given as the mean of the 16 items giving an overall scale of 0-10	Difference of 0.5 points (SD=2)	550	Cohen 2006 (55) indicated a 1pt difference between a 'bad' and 'average' day or 'average' and 'good' day; using this would reduce the sample size to 140.
If feasible, **Time to symptom relief**	Continuous outcome based on the number of minutes from when the need for symptom relief is noted until the time symptoms are resolved.	10 minutes (SD = 35 minutes)	520	To achieve 90% power to detect a difference of this size with a significance level of 0.05 using a two sided test

Planned recruitment rate

Fifty of the dyads will be in the intervention arm and 50 in the control arm (that is, 16-17 per arm in each area). 25 in each arm (50 in total) is envisaged to be able to complete the trial (that is, 8-9 per arm per area): 50 completers are needed for the analysis.

Monthly, each of the three sites will need to approach 5 to 6 dyads, consent 2 to 3, with 1 to 2 completing the trial. This will equate to, per site over the 12 month recruitment period, approaching 66-67, consenting 34 and aiming for 17 dyads to complete the trial.

Background:
Patients dying at home as per their expressed wish, in the proposed areas of recruitment:

- As per the 2013 ONS data, we know that 8.58% of all deaths are home deaths of neoplasms in those aged over 15. (54) [Neoplasm deaths are used as a proxy for expected deaths of all causes]
- Therefore, the 3 recruitment areas have the following numbers available per annum – North Wales 653, Gloucestershire 517, Cardiff and the Vale 349.

Lay carers of patients cared for at home in their last days of life:

- Drawing on the collective clinical experience of the project team, we know that it is rare for a patient to successfully fulfil their wish to die at home if they do not have the support of a lay carer. This is due to the fact that most health and care services (also, specifically in the areas we propose to recruit from) cannot provide 24/7 care in a patient's own home.
- That said, the best data available on this topic comes from a recent quasi-experimental study examining palliative care interventions at home. It noted that of 953 patients expressing a preference to die at home 72.2% had an informal carer. (56) It is worth noting that the study did not record where patients who were unable to identify an informal carer actually died, or whether previously unidentified lay carers in the patient's circle stepped in to support their wish to die at home.

For the pilot trial,

- We propose to approach 200 dyads (66-67 in each area) over a period of 12 months.
  So, even if only 72.2% of patients have an identified carer, the figures of dyads in the three areas that could be eligible are – North Wales 471, Gloucestershire 373, Cardiff and the Vale 251. It is also worth noting that all the participants in the focus group indicated they would take part in a trial if offered (caution: selection bias)
- Of whom, on very conservative calculation, 100 will consent to participate (33-34 in each area).
  The percentage recruited in the Australian study was much higher, 97.6% of those approached consented to participate
- 50 of those will be in the intervention arm (receiving training) and 50 in the control arm (that is, 16-17 per arm in each area)
- With, again on very conservative calculation, 25 in each arm (50 in total) will complete the trial (that is, 8-9 per arm per area)

50 completers are needed for the analysis: i.e. 25% of those initially approached for participation.

b. Statistical analysis plan

A full statistical analysis plan will be written, agreed and signed off before data collection has been completed. All co-applicants will have the opportunity to feed into this analysis plan. Both independent committees will have the opportunity to comment on this plan before sign off.
Primary analysis will be concentrated on the feasibility metrics and adherence outcomes based on the thresholds defined in Table 3. There will be limited preliminary analysis of intervention outcomes. Point and 95% confidence interval estimates will be calculated and used to estimate variability and direction of effect to further inform the sample size calculation for a definitive study.
Summary statistics of all outcomes will be used to inform the approximate models of analysis that would be used in a full trial. It is hard to specify models until the data is better understood through the feasibility trial, (e.g. numbers of episodes where as-needed medication used, proportion of participants that never required as-needed medication). A preliminary analysis of the outcomes will be completed using an intention to treat approach.
As this is a feasibility trial there will be no imputation of missing data. Missing data will be considered as a criteria for assessing the suitability of measures. Descriptive statistics will be produced for each of the outcome measures, to evaluate the appropriateness of the measures for inclusion in a full RCT.

Progression to full trial
Clear progression rules are defined to determine whether an application for a future substantive trial powered to study effectiveness and cost effectiveness should proceed. Our progression rules will relate to the following measures; which we considered important to feasibility:
- reaching our target (16.6) for the number of patients recruited ***per site*** within 12 month frame.

We have also established clear assessment criteria for establishing the acceptability of the potential primary outcome measures.
The table below summarises the objectives, action plan and criteria for progression to a full trial.

Table 3: Objectives, action plan and criteria for progression to a full trial

Objectives	Action Plan	Threshold for progression to full RCT
1 To refine the assessment and outcome measures to be used in any potential RCT	Qualitative feedback will be collected from participants 2-4 months after the intervention, regarding the acceptability of the measures and will evaluate whether all of the intended information was captured.	
2 To evaluate the acceptability of the manualised intervention (and potentially refine).	An expert consensus group will refine trial processes, education package and resources (Hurt 2013). An initial workshop with Australian team (completed Nov 2015) A detailed process in the study protocol clarifying the legal and regulatory framework for the practice	In the feasibility study the simplest method is for lay carers to draw up meds only in immediate form; a full trial would be more appropriate if able to extend this to advanced preparation and labelling

3 To evaluate the recruitment process	Referral sites and referral sources Where participants heard about the study Number and speed of referrals received and time elapsed between initial contact made with the study team (for information and consent form),	In the feasibility we have assumed 50% recruitment – We would say a full trial is not possible if recruitment falls below 30%,
4 To estimate participant retention rate for the full RCT	Retention rates will inform the refinement of the sample size calculation for any potential subsequent RCT. Participant engagement will be monitored throughout the pilot trial	In the feasibility we have assumed 50% recruitment – we would say a full trial is not possible if recruitment falls below 40%
5 To test the assessment and outcome measures for suitability, relevant change factors, and acceptability to participants.	Data from the assessment process will be compared against raw data from the outcomes measures to assess the outcome measures sensitivity to identifying participant change.	
6 To identify acceptability and collection of relevant data to inform the data collection and analysis plan for implementation in the subsequent RCT.	A review will be completed of each outcome measure of levels of missing data and stability to ensure that the information collected will allow any future main analysis to be feasible and appropriate. Amendments can be suggested where appropriate to amend data collection for any potential future trial. The data available will also inform the details for the analysis plan of any potential full trial.	Carer Diary data items successfully completed (70%) Family MSAS-GDI successfully completed at bereavement visit (70%) QOLLTI-F successfully completed at 48 hr intervals (70%)

c. Economic evaluation

While the DCE will be conducted as part of a future main study, the preparatory work required to identify relevant attributes and levels will be done as part of the qualitative interviewing component of the project. For more detail, please see earlier section on 'Work-up towards future Discrete Choice Experiment (DCE)'.

8. TRIAL MANAGEMENT

a. Trial Management Group (TMG)

The TMG includes a multidisciplinary team with considerable trials expertise. We plan to hold these meetings alternate months.
There is also a weekly operational group meeting.

b. Trial Steering Committee (TSC)

The TSC will have an independent Chairperson (Professor David Weller) and at least three independent members including PPI representation and trial co-applicants.
Our independent members include Professor Tim Peters (Bristol University), Dr Christine Hirsch (Birmingham University), and Dr Catriona Mayland (University of Liverpool).

Meetings are scheduled bi-annually, routine business will be conducted by email. The TSC, throughout the trial will take responsibility for:

- Major decisions
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the TAG
- Considering recommendations from the DMEC
- Informing and advising on all aspects of the trial

Professor Weller has expertise in community based cancer research, and conducting randomised trials in community settings. Our independent members have been chosen for their relevant expertise, Professor Tim Peters is a statistician, Dr Christina Hirsch is an academic pharmacist with palliative care expertise and Dr Catriona Mayland is an academic palliative care physician.

c. Data Monitoring and Ethics Committee (DMEC)

The DMEC will have an independent Chairperson (Professor John Ellershaw, University of Liverpool) and other independent members include Professor Ceri Phillips (University of Swansea), Dr Wei Gao (King's College London), and Professor Mari Lloyd-Williams (University of Liverpool) will meet bi –annually.

The DMEC will review trial progress, in line with the trial timetable and monitoring policy. The DMEC will advise appropriately on cessation or continuance of the trial. It will advise the TSC, based on the trial data monitored and any future publications or emerging worldwide evidence. DMEC meetings will also be attended by the Chief Investigator and Trial Manager (for non-confidential parts of the meeting) and the trial statistician.

Professor Ellershaw has expertise in palliative care research and ethical considerations regarding dying patients, and the other independent members have been chosen for their various expertise. Professor Ceri Phillips has health economic expertise, Professor Wei Gao is able to provide an independent statistical view, and Professor Marie Lloyd-Williams a palliative care angle.

9. ETHICAL AND REGULATORY CONSIDERATIONS

Overall ethical and consent issues in palliative care trials:

- We will work within the bounds of the Mental Capacity Act, England and Wales (2005), (57) and with full cognisance of the MORECare guidelines (29) (58) to ensure we address ethical issues in depth throughout the project.
- Advanced consent from both the patient and their lay carer at a time point judged to be suitable for discussion by the attending physician or nurse, when the patient is in the dying phase, e.g. a number of weeks anticipated life. This gives the patient a chance to make their feelings clear on trial participation and inform the subsequent discussion with the Personal Consultee.
- Even if the patient has consented, once they lose capacity, a Personal Consultee (as required by the MCA) will need to give their assent. (59) We would prefer the Personal Consultee NOT to be the same carer, as it is possible to imagine rare circumstances when that lay care could be conflicted. This will ensure families and participating communities of a robust ethical approach.
- In the circumstance when there is no additional family member or close friend to act as the Personal Consultee, we will seek to appoint a Nominated Consultee (e.g. a member of hospice staff not associated with the research) who may be able to act for all patients in this circumstance in the trial.

Recruitment of lay carers for training

- Clinical judgement as well as ethical considerations also need to be utilised when assessing the appropriateness of individual lay carers to draw up and administer medications in the first instance.

Research Ethics Committee (REC) review& reports

Before the start of the pilot trial, approval will be sought from an NHS REC flagged to review studies involving Adults Lacking Capacity (possibly one with expertise in reviewing palliative care projects) for the trial protocol, informed consent forms, information sheets and other relevant documents e.g. interview topic guides. Any changes required by the REC will be discussed with the study team and PPI representatives and the funder before formally replying to the Committee's requests for further information or clarification.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. The Cis will submit a final report with the results, including any publications/abstracts, to the REC within one year after the end of the study.

Peer review

This protocol has had high-quality (independent, expert and proportionate) peer review through the NIHR HTA funding application process. The independent members of the TSC and DMEC will provide an element of continuous peer review.

Public and Patient Involvement

Our team is committed to meaningful involvement of patient representatives. Two service users are co-applicants. Insights gained from their experiences of giving injections to dying loved ones at home were crucial in designing the project. They have offered to be involved at all stages of the project. Their involvement will be fundamental in disseminating the research results to patients, carers and healthcare professionals. Two

additional groups of bereaved carers have been consulted and their suggestions on consent mechanisms, drug safety, training and ongoing support have been incorporated into the study design.

The Palliative and End of Life Care Priority Setting Partnership report (produced in Jan 2015 with significant input from public contributors) placed great emphasis on good symptom control, irrespective of setting or time of day, and called for the empowerment of family/carers to support their loved one in the place of their choice. (13) Our proposed work fits exactly into this remit, specifically numbers 1 and 4 of the top 10 unanswered research questions in palliative care.

The recruitment of representatives with appropriate and explicit experience ensures that we fully understand the needs of our research participants.

The project will be supported by the Wales Cancer Research Centre, which is currently finalising a framework for PPI that will comprise standard operating procedures for recruitment, training, mentoring, finance, induction and monitoring of PPI representatives, minimum standards for PPI, and a newly developed PPI impact measurement tool. Importantly, the framework will also introduce training for researchers, and a 'joint commitment' for researchers and PPI representatives to aid mutual expectations of their roles. This framework is co-led by a member of the research team (AN), mentored by Simon Denegri from Involve, England, and builds on previous published work in PPI for trials and academic units.
In line with the framework, the PPI representatives will be invited to join the Involving People network in order to benefit from its training portfolio and support systems. All usual arrangements, refreshments, travel, access and carer support, will be in place for considerate inclusion of PPI representatives at meetings.

Regulatory Compliance

Before any site can enrol patients into the trial, the CI/PI or designee will apply for NHS permission from the site's R&D department. For any amendment that will potentially affect a site's NHS permission, the CI/PI or designee will confirm with that site's R&D department that NHS permission is ongoing. (It is understood that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D).

Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and will not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.
Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and will be reported to the Sponsor immediately.
Deviations from the protocol will be monitored. Frequently recurring deviations will require immediate action and could potentially be classified as a serious breach.

A trial specific adaption to NWORTH's SOP 4.05 'Deviation, misconduct and serious breaches' will detail the reporting procedure for trial related deviations, to include identification of the deviation, details of initial corrective actions and assessment of impact on trial participants. The trial manager will be responsible for setting up such a reporting procedure.

Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

We will notify the sponsor immediately of any case where the above definition applies during the trial conduct phase.

The sponsor will notify the appropriate NHS organisation in writing of any serious breach of

- the conditions and principles of GCP in connection with that trial; or
- the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

We will ensure that all investigators and trial site staff have up-to-date GCP training.

Staff will be trained in the means whereby personal information is collected, kept secure, and maintained. In general, this involves:

- the creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters
- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis

Training will also include how the confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators.

Research data will be retained as per the sponsor's research data management policy. Bangor University is the data custodian.

Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The CIs and co-applicants have no conflicts or potential conflicts of interest in undertaking this research. Although we are not aware of any conflicts of interest amongst our independent committee members we will seek to confirm this at the outset of the project.
At the time of writing the protocol not all study personnel have been identified. Information on financial and competing interest of new staff will be collected and documented in our central filing system. The TSC will determine what it is appropriate to report.

Indemnity

1. Arrangements for insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research:
   This is the sponsor's responsibility, and is provided for under sponsor's Public Liability cover for any negligent acts or omissions of the sponsor or its staff involved with the management of the research.

2. Arrangements for insurance and/ or indemnity to meet the potential legal liability of the sponsor or employer(s) for harm to participants arising from the design of the research:
   This is the sponsor's responsibility, and is provided for under the sponsor's Professional Indemnity cover for any negligent acts or omissions of the sponsor or its staff involved with the design of the research

3. Arrangements for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

   This is the responsibility of each participating site and evidence of those sites indemnity covers should be provided.
   Sites that are not covered by the NHS indemnity scheme (e.g. GP surgeries in primary care) investigators/collaborators will need to ensure that their activity on the study is covered under their own professional indemnity.

Documents provided by the sponsor's insurers to furnish evidence of the relevant cover will be made available on request.

Amendments

All suggested protocol changes will, in the first instance, be notified to the HTA Research Manager via the online 'Update Protocol' task, prior to any changes being made. Once the changes have been approved by the funder, the REC and NHS R&D departments will be notified as appropriate (as per the definitions of substantial and non-substantial amendments and guidance on www.hra.nhs.uk/resources/after-you-apply/amendments).

If a substantial amendment needs to be made to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide (with agreement from the funder) whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments also need to be notified to NHS R&D departments of participating sites to assess whether the amendment affects the NHS permission for that site. Some amendments that may be considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

The amendment history will be tracked to identify the most recent protocol version.

Post trial care

The patients who took part in the trial would have died (as they are followed up as part of the trial until death). Participating family members/lay carers will be interviewed 2-4 months post-bereavement.

As part of the REC application arrangements for dealing with substantial, ongoing distress in bereaved carers will be detailed. This will include

- strategies during the interviews (sensitive questioning, reassurance, reiterating the options to stop or postpone the interview at any time),
- and for follow-up (advice to contact own primary care team or, in the event of concerns raised regarding severe mental health issues such as expression of suicidal intent the researcher to discuss with the carer's primary care team)

Agreement for this process is to be obtained via the consent mechanism.

Access to the final trial dataset

Access to the final dataset will be in accordance with governance policies, GCP guidelines and NIHR arrangements.

The trial statisticians will have full access to the dataset.
The CIs and trial manager will have access to the full dataset after the analysis has been completed.
The DMEC will have access to the full dataset as required.
The TSC will have access to the full dataset prior to the individual sites having access.

10. QUALITY ASSURANCE AND QUALITY CONTROL

a. Monitoring, Audit & Inspection

A Trial Monitoring Plan will be developed and agreed by the TMG and TSC based on the trial risk assessment. Site monitoring will be done by performing site visits (at least once per site, with a specific focus on consent recording and handling of data and site files) as well as remotely by exploring the trial dataset.

The sites will be expected to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally. Monitoring will be conducted across all sites, and will include a focus on enrolment rates, numbers of withdrawals, and numbers of reported adverse events.

Responsibilities for monitoring will be defined and documented in the Trial Monitoring Plan.

The procedure for authorisation of participating sites is detailed in Appendix 5.

11. DATA HANDLING

a. Data collection tools and source document identification

Source data will be captured on paper at the relevant time points. A study specific MACRO database will be developed to allow researchers to enter data online. MACRO allows controlled access to the data by all centres and stores a full audit trail. The electronic data captured in the MACRO database will be stored on servers maintained by Bangor University and will be subject to the university IT disaster recovery procedures.

b. Access to Data and data management

Paper data at sites will be stored in locked filing cabinets separately from identifiable participant data. Access to the MACRO site will be secure and password controlled.
Access to MACRO will be defined on two different levels, access to input (researchers at sites) and access to full data set which will be limited to those core team members involved in data and trial management.
A detailed data management plan will be written and will include the definition of the data quality checks that will be performed on the data throughout the life course of the trial. These will include source data validation, random data checks and timelines for data entry.

c. Data sharing

During the course of the trial data sets may be requested from the trial team. A data request form will form part of the data management plan and will document the approval and retrieval process for data sets during the conduct of the trial. All requests will have to be approved by the CI. All data requests and data sets issued will be retained for completeness.

d. Data archiving

Archiving of trial documents will be authorised by the Sponsor following submission of the end of study report. As per the sponsor's research data management policy, research data and records will be retained "for as long as they are of continuing value to the researcher and the wider research community, and as long as specified by research funder, patent law, legislative and other regulatory requirements. The minimum institutional retention period for research data and records is five (5) years after publication or public release of the work of the research, unless required by the funder to retain for longer." (60)

In line with legal requirements, trial documents will be archived centrally at a secure facility with appropriate environmental controls and adequate protection from fire, flood and unauthorized access. Archived material will be stored in tamper- proof archive boxes that are clearly labelled.

Electronic archiving will be provided by the sponsor for post-project deposit and retention of data.

Destruction of essential documents will require authorisation from the Sponsor.

12. DISSEMINATION POLICY

Dissemination policy

The results of the study will be firstly reported to trial collaborators. The main report will be drafted and agreed by the trial co-ordinating team and the final version will be agreed by the HTA before submission for publication, on behalf of the collaboration.

The study findings will be disseminated through publication in highly cited and open access peer reviewed journals and submissions to national and international conferences. In addition, dissemination of our work to clinical and academic colleagues will be via professional societies, newsletters, existing networks and professional web-sites. Relevant NHS organisations and healthcare providers e.g. Clinical Commissioning Groups and NICE will be informed of the study outcomes.

All carer participants, if they so wish, will be sent an accessible summary of the findings from the study that they took part in within six months of study completion. The same summary will be made available to public/patient forums to inform patient groups across the area.

It is expected that the steering group associated with the study will ensure a high level of awareness of our work in the relevant media whilst exploring the use of social media to disseminate outcomes, encourage public/patient involvement and promote future research to improve patient care at the end of life.

Expected Output of Research/Impact

Outputs include the following:

- A training package for health care professionals to 'train the carers' regarding SC medication administration.
- A standardised, manualised training package for UK lay carers re SC medication administration in the home.
- Establishment of whether or not feasible to roll out a full RCT of effectiveness and cost –effectiveness.
- Publication in peer reviewed journals.
- An exemplar of highly integrated and pro-active PPI role in care of the dying trials.

Impact includes the following:

Successful carer-administration of as-needed SC medication for breakthrough symptoms in a dying patient is likely to have impact at various levels.

At patient and family level:

- improve the quality of experience (and thus increase the likelihood of a 'good death') for the patient who chooses to be at home by providing speedier symptom control and supporting their wish to die at home.
- empower lay carers through the personal fulfilment of having supported a patient's wish to stay at home; increase satisfaction and reduce anxiety and frustration related to poor symptom control.
- increase lay carer confidence and competence in caring for a dying loved one.

At NHS Community staff level:

- enhance teaching and training skills of DN staff.
- free up community staff time to address other needs of patients and families.
- contribute to sustainability of services.

At NHS Hospital staff level:

- reduce inappropriate emergency (crisis) admissions due to uncontrolled symptoms and its associated costs.

At wider societal levels:

- if generalisability from Australia is demonstrated in the UK, this could spread to other countries with similar healthcare systems.
- provide an exemplar for conducting randomised controlled trails in the last days of life by contributing to the emerging methodological development of palliative care research.
- enable dying well to be less medicalised and more home based if that is the person's choice.

Authorship eligibility guidelines and any intended use of professional writers

Authorship (individually named or group) on the final trial report and manuscripts submitted for publication will be in accordance to the authorship criteria defined by the International Committee of Medical Journal Editors. (61)

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Professional medical writers will not be used.

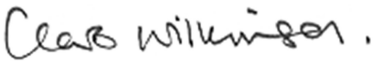
13. FINANCIAL AND INSURANCE ASPECTS

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
National Institute for Health Research (Health Technology Assessment) United Kingdom	Research costs £490,853.46
NHS recruitment sites: Betsi Cadwaladr University Health Board Cardiff & Vale University Health Board Gloucester Care Services NHS Trust	NHS Support & Treatment costs £28,414.25

14. APPROVAL SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended. 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 clinical investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publically 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: 06/06/2017
.....
Name (please print):
.....Professor Christopher R Burton.....
Position:
..... Head of School, School of Healthcare Sciences.....

Chief Investigator:
Signature:  Date: 06/06/2017
.....
Name: (please print):
.....Professor Clare Wilkinson.....

Chief Investigator:
Signature:  Date: 06/06/2017
.....
Name: (please print):
.....Dr Marlise Poolman.....

Senior Statistician:
Signature:  Date: 06/06/2017
.....
Name: (please print):
.....Dr Zoë Hoare.....
Position:
.....Principal Trial Statistician.....

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16. APPENDICES

a. Appendix 1 – Legal framework

Clarity on legal issues is a significant aspect of this research to ensure lay carers and clinicians alike have legal protection. Our Australian partners have given us full access to their reference resource. (62) Their document covers a broad range of topics on the handling of medication in community-based palliative care services, but, specifically, details medication management, drug storage (security of medications, individual responsibility for medication storage and security, individual disposal of medication), prescribing, and medication administration (who can administer? including role of lay carer, record of administration) in the context of lay carer administration.

The premise:
A lay carer can legally administer individually prescribed medication for a third party, including controlled drugs such as morphine, as long as the carer has been appropriately trained and assessed as competent, specifically in medication management. This is true even if the medication is given to a patient lacking capacity, and/or if the medication is administered via injection. At present, injections are prepared immediately before administration (and not in advance, requiring relabelling). Carers should be trained to assess symptoms and should have access to dedicated support.

In support of these statements, the relevant sections from UK legislation and guidance are detailed below:
A lay carer can administer individually prescribed medication for a third party, including controlled drugs such as morphine,

- Section 7(3) of the Misuse of Drugs Regulations 2001 states "*Any person other than a doctor or dentist may administer to a patient, in accordance with the directions of a doctor or dentist, any drug specified in Schedule 2, 3 or 4.*" (63)
- This was confirmed by the UK Medical Defence Union. (64)
- NHS NPC guidance (2009)"*A carer/relative can, with consent, administer a controlled drug (CD) that has been individually prescribed for a third party. As CDs are included within the legal category of prescription-only medicines (POMs), home carers who are competent to administer medicines should also be competent to administer CDs*" (65)
- Morphine is listed in Schedule 2, and Midazolam in Schedule 3. (66)

As long as the carer has been appropriately trained and assessed as competent,

- Nursing & Midwifery Council (NMC) guidance, Standard 17: Delegation: "*A registrant is responsible for the delegation of any aspects of the administration of medicinal products and they are accountable to ensure that the patient, carer or care assistant is competent to carry out the task. This will require education, training and assessment of the patient, carer or care assistant and further support if necessary. The competence of the person to whom the task has been delegated should be assessed and reviewed periodically. Records of the training received and outcome of any assessment should be clearly made and be available.*" (67)
- "*home carers who are appropriately trained and assessed as competent are authorised to administer orally prescribed controlled drugs*" (68)
- "*The cornerstone of the policy is a risk assessment to identify appropriate support for service users and the provision of appropriate training for those staff that will assist service users with medication. A*

carer administering a medicine will not be held responsible for any adverse effects, providing a medicine has been given in accordance with a prescriber's instructions and local policies have been followed. Employing organisations should include medication tasks in any indemnity insurance they arrange." (69)

Specifically in medication management.

- *"Carers will operate within a safe system which will be based on a risk assessment and this will need to be underpinned by a structured programme of education and learning in the safe handling, administration and management of medication."* (69)
- Procedures are already in place in the UK to handle/store medications (including for anticipatory care purposes) in the patient's home (35)

This is true even if the medication is given to a patient lacking capacity,

- Medication can be given to a patient who lacks capacity if it is in his or her best interests. The Mental Capacity Act (MCA) 2005 Section 1(5) states: "*An act done, or decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made, in his best interests*." (70)
- The MCA 2005 permits the relevant actions to be performed by those with appropriate skills or expertise (as long as the carer has been appropriately trained and assessed as competent). The Code of Practice explains: "*To receive protection from liability under section 5, all actions must be related to the care or treatment of the person who lacks capacity to consent. Before taking action, carers must first reasonably believe that:*
    - *the person lacks the capacity to make that particular decision at the time it needs to be made, and*
    - *the action is in the person's best interests.*" (57)

And/or if the medication is administered via injection.

- For specialist tasks (including injections) a suitable health professional needs to give additional training and confirm that the carer is competent to provide such care. (69)

At present, injections are prepared immediately before administration

- NMC Guidance, standard 14: "*Registrants must not prepare substances for injection in advance of their immediate use or administer medication drawn into a syringe or container by another practitioner when not in their presence*." (67) It follows with guidance: "*Where a registrant has delegated to a named individual for a named patient's medication, this may be drawn up in advance to enable the healthcare assistant (HCA) or family to administer the medication. The registrant is accountable for the delegation, and a full risk assessment should be documented in the patient's records ensuring the registrant is aware of the risks before agreeing to delegate.*"
- Note: There is evidence that the practice of drawing up and leaving these medications in syringes, for this type of practice, is safe in terms of sterility, potency and stability. (71) The team tested a full range of medications for 28 days.

Carers should be trained to assess symptoms, use the least invasive methods of administration and should have access to dedicated support.

b. Appendix 2 – Clinical Trial Authorisation requirements

From: Clinical Trial Helpline <ctdhelpline@mhra.gsi.gov.uk>
Date: 29 October 2015 at 14:19:55 GMT
To: Clare Wilkinson <c.wilkinson@bangor.ac.uk>

Subject: RE: Scope - protocol review: CARer-ADministration of as-needed sub-cutaneous medication for breakthrough symptoms in homebased dying patients: a UK study (CARiAD*)
Notification that a Clinical Trial Authorisation (CTA) is not required

Dear Ms Wilkinson

Thank you for your email dated 20 October 2015.
I can confirm that your proposal is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC and no submission to the Clinical Trials Unit at the MHRA is required.
Kind regards

Clinical Trial Helpline
MHRA

From: Clare Wilkinson [mailto:c.wilkinson@bangor.ac.uk]
Sent: 20 October 2015 16:26
To: Clinical Trial Helpline
Cc: Clare Wilkinson
Subject: Scope - protocol review: CARer-ADministration of as-needed sub-cutaneous medication for breakthrough symptoms in homebased dying patients: a UK study (CARiAD*)

Dear MHRA Experts,

Please could you help us to determine whether our feasibility trial is a CTIMP? The HTA has approved this outline proposal to proceed to a full application.

We are proposing to text the extended role of lay/family carers in last days of a person's life at home, by training them to give as-needed sub-cutaneous medications for breakthrough symptoms. The situation often arises that there is a syringe driver in place, but someone needs to give relief medication, and this person is usually a District Nurse, but this takes time.
All these meds are routinely used all over the UK at this point in the dying process, to relieve symptoms when the oral route isn't possible anymore. This project is about allowing the care to happen in the person's home. So, the drugs themselves are not the focus of the study, nor the route (in this instance likely SC when the oral route is lost), but rather the way in which the drugs are administered (by trained and supported carers rather than Health Care Professionals; this is a common practice in Australia and indeed some areas of the UK)

Some of the drugs are not licensed for SC use, but are part of standard care suggested by UK national guidelines (British National Formulary, Palliative Care Formulary)

Palliative care resources and the drug SPCs: (on the specific issue if each is licensed for SC (sub-cutaneous) use, and for interest CSCI (continuous sub-cutaneous infusion)

- Diamorphine is indeed licenced for SC and CSCI
- Morphine sulphate is licenced for SC but not CSCI
- Cyclizine is not licensed for either SC or CSCI
- Midazolam is not licensed for either SC or CSCI

What we are less clear about it the exact impact if drugs are used unlicensed (without market authorisation), versus off-label (beyond market authorisation) on the decision that it is a CTIMP or not.

We would be most grateful for an early answer,
Kind regards
Clare Wilkinson

c. Appendix 3 - Outcome measures

Carer Diary – Intervention group

Date and time that symptom developed	Breakthrough symptom	Symptom score before (0-10)	Medication given	Dose	Time medication was given at	Symptom score 30 minutes after medication (0-10)	When were symptoms resolved to an acceptable level?	How confident were you in giving the injection? (1-7)	Was healthcare professional support sought?
__/__/__ ____:____ am/pm Noted by: ☐ Patient ☐ Carer	☐ Pain ☐ Nausea /vomiting ☐ Agitation ☐ Noisy breathing	Assessed by: ☐ Patient ☐ Carer ☐ HCP	Name: Given by: ☐ Carer ☐ HCP		____:____ am/pm	____ / 10 Assessed by: ☐ Patient ☐ Carer ☐ HCP	☐ Within 30 mins of medication ☐ If longer please specify time: _____ Assessed by: ☐ Patient ☐ Carer ☐ HCP		☐ Yes ☐ No
Comments									

To be completed by HCP if applicable:	HCP details (Name, profession, signature)	Time attended:	Assessment made:	Outcome:

Carer diary – Control group

Date and time that symptom developed	Breakthrough symptom	Date and time healthcare professional (HCP) was contacted:	Symptom score when HCP was called (0-10)	Time HCP arrived:
__/__/__ ___:____ am/pm Noted by: ☐ Patient ☐ Carer ☐ HCP	☐ Pain ☐ Nausea or vomiting ☐ Agitation ☐ Noisy breathing	__/__/__ ___:___ am/pm	____ / 10 Assessed by: ☐ Patient ☐ Carer ☐ HCP	___:___ am/pm
Medication given	**Dose**	**Time medication was given at**	**Symptom score 30 minutes after medication (0-10)**	**When were symptoms resolved to an acceptable level?**
Name:		___:___ am/pm	____ / 10 Assessed by: ☐ Patient ☐ Carer ☐ HCP	☐ Within 30 mins of medication ☐ If longer please specify time: Assessed by: ☐ Patient ☐ Carer ☐ HCP
Comments:				

HCP details (Name, profession, signature)	Comments:

Family MSAS-GDI

Family Memorial Symptom Assessment Scale Global Distress Index (Family MSAS-GDI)

TELEPHONE SURVEY DIRECTIONS: **"I am going to ask you about specific symptoms <insert decedent's name> may have had in the last week of his/her life."**

Part A: Psychological Symptoms

SYMPTOM	A. ASK "Did he/she seem to _____ in the last week of his/her life?" IF "No," SCORE A AND B AS "0" AND SKIP TO NEXT ITEM NUMBER. IF RESPONDENT UNABLE TO COMMENT ON AFFECT BECAUSE DECENDENT UNRESPONSIVE IN LAST WEEK OF LIFE, SCORE #1-4 AS N/A AND SKIP TO #5 B. IF "Yes" THEN ASK "How often did he/she _____?"	IF "N/A" (not applicable), "D/K" (don't know), OR "Refusal," SKIP TO NEXT ITEM NUMBER.
1. A Did he/she seem to *FEEL SAD*?	0 No (SCORE B AS 0, SKIP TO #2) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How often?	0 Never / 1 Rarely / 2 Occasionally / 3 Frequently / 4 Almost constantly	7 N/A 8 D/K 9 Refusal
2. A. Did he/she seem to *WORRY*?	0 No (SCORE B AS 0, SKIP TO #3) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How often?	0 Never / 1 Rarely / 2 Occasionally / 3 Frequently / 4 Almost constantly	7 N/A 8 D/K 9 Refusal
3. A. Did he/she seem to *FEEL IRRITABLE*?	0 No (SCORE B AS 0, SKIP TO #4) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How often?	0 Never / 1 Rarely / 2 Occasionally / 3 Frequently / 4 Almost constantly	7 N/A 8 D/K 9 Refusal
4. A. Did he/she seem to *FEEL NERVOUS*?	0 No (SCORE B AS 0, SKIP TO #5) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How often?	0 Never / 1 Rarely / 2 Occasionally / 3 Frequently / 4 Almost constantly	7 N/A 8 D/K 9 Refusal

Part B. Physical Symptoms

SYMPTOM	A. ASK "Did < > seem to (have)_____ in the last week of his/her life?" IF "No," SKIP TO NEXT ITEM NUMBER. B. IF "Yes" THEN ASK "How much did that distress or bother him/her?"	IF "N/A" (not applicable), "D/K" (don't know), OR "Refusal," SKIP TO NEXT ITEM NUMBER.
5. A. *LACK OF APPETITE*?	0 No (SCORE B AS 0, SKIP TO #6) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How much did that distress him/her?	0 Not at all / 1 A little bit / 2 Somewhat / 3 Quite a bit / 4 Very much	7 N/A 8 D/K 9 Refusal
6. A. *LACK OF ENERGY*?	0 No (SCORE B AS 0, SKIP TO #7) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How much did that distress him/her?	0 Not at all / 1 A little bit / 2 Somewhat / 3 Quite a bit / 4 Very much	7 N/A 8 D/K 9 Refusal
7. A. *FEEL DROWSY*?	0 No (SCORE B AS 0, SKIP TO #8) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How much did that distress him/her?	0 Not at all / 1 A little bit / 2 Somewhat / 3 Quite a bit / 4 Very much	7 N/A 8 D/K 9 Refusal
8. A. *CONSTIPATION*?	0 No (SCORE B AS 0, SKIP TO #9) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How much did that distress him/her?	0 Not at all / 1 A little bit / 2 Somewhat / 3 Quite a bit / 4 Very much	7 N/A 8 D/K 9 Refusal
9. A. *DRY MOUTH*?	0 No (SCORE B AS 0, SKIP TO #10) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How much did that distress him/her?	0 Not at all / 1 A little bit / 2 Somewhat / 3 Quite a bit / 4 Very much	7 N/A 8 D/K 9 Refusal
10. A. *DIFFICULTY BREATHING*?	0 No (SCORE B AS 0, SKIP TO #11) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How much did that distress him/her?	0 Not at all / 1 A little bit / 2 Somewhat / 3 Quite a bit / 4 Very much	7 N/A 8 D/K 9 Refusal
11. A. *PAIN*?	0 No (SCORE B AS 0) / 1 Yes (ASK B)	7 N/A 8 D/K 9 Refusal
B. How much did that distress him/her?	0 Not at all / 1 A little bit / 2 Somewhat / 3 Quite a bit / 4 Very much	7 N/A 8 D/K 9 Refusal

QOLLTI-F

QOLLTI-F©: Quality of Life During Serious Illness – Family Carers

STUDY IDENTIFICATION #: _____ DATE: _____

Day/Month/Year

PLEASE READ THESE INSTRUCTIONS BEFORE ANSWERING THE QUESTIONNAIRE

There are no right or wrong answers. Honest answers will be most helpful.
This questionnaire includes a series of statements that we would like you to respond to by choosing a number from 0 to 10.
These numbers extend from one extreme answer (for example, 'not at all') to its opposite (for example, 'completely').
Please choose or circle the number between 0 and 10 that best represents how you feel.

Note that sometimes the best situation is at the 0 end of the scale, and sometimes the best situation is at the 10 end of the scale.

We are interested in learning about your OVERALL quality of life, so please consider any issues that affect you, even if they are not related to your caregiving role.

A blank in a sentence refers to the person you are caring for, but please do not write any name to keep this confidential.

1. Over the past two days (48 hours) I wondered if the place _____ was staying (home, hospital, other) was the right place to be:

never 0 1 2 3 4 5 6 7 8 9 10 always

2. Over the past two days (48 hours) I had the privacy I wanted:

not at all 0 1 2 3 4 5 6 7 8 9 10 completely

3. Over the past two days (48 hours) the condition of _____ was distressing to me:

not often 0 1 2 3 4 5 6 7 8 9 10 always

4. Over the past two days (48 hours) the amount of control I had over my life was:

not a problem 0 1 2 3 4 5 6 7 8 9 10 a huge problem

5. Over the past two days (48 hours) I had time to take care of myself:

never 0 1 2 3 4 5 6 7 8 9 10 always

6. Over the past two days (48 hours) I was able to think clearly:

not often 0 1 2 3 4 5 6 7 8 9 10 always

7. Over the past two days (48 hours) physically I felt:

extremely poor 0 1 2 3 4 5 6 7 8 9 10 extremely good

8. Over the past two days (48 hours) emotionally I felt:

extremely poor 0 1 2 3 4 5 6 7 8 9 10 extremely good

9. Over the past two days (48 hours) being able to provide care or company for_____ made me feel good:

rarely or never 0 1 2 3 4 5 6 7 8 9 10 always

10. Over the past two days (48 hours) I was comforted by my outlook on life, faith, or spirituality:

not at all 0 1 2 3 4 5 6 7 8 9 10 completely

11. Presently I feel that my life has meaning:

very little meaning 0 1 2 3 4 5 6 7 8 9 10 very much meaning

For questions 12 and 13, if you did not make important decisions or need health care in the past two (2) days, please answer for the last few times you did.

12. Over the past two days (48 hours) I agreed with the way decisions were made for _____:

not at all 0 1 2 3 4 5 6 7 8 9 10 completely

13. Over the past two days (48 hours) the quality of health care we received was:

unsatisfactory 0 1 2 3 4 5 6 7 8 9 10 extremely good

14. Over the past two days (48 hours) I felt my interaction with _____ was:

very comfortable 0 1 2 3 4 5 6 7 8 9 10 stressful

15. Over the past two days (48 hours), overall, I felt my interactions with the other people most important to me were:

very comfortable 0 1 2 3 4 5 6 7 8 9 10 stressful

16. Over the past two days (48 hours) my financial situation has been stressful:

not at all 0 1 2 3 4 5 6 7 8 9 10 completely

Carer Experience Scale

PLEASE TICK ONE BOX FOR EACH GROUP to indicate which statement best describes your current caring situation.	
1. Activities outside caring ***(Socialising, physical activity and spending time on hobbies, leisure or study)***	
You can do most of the other things you want to do outside caring	☐ 1
You can do some of the other things you want to do outside caring	☐ 2
You can do few of the other things you want to do outside caring	☐ 3
2. Support from family and friends ***(Personal help in caring and/or emotional support from family, friends, neighbours or work colleagues)***	
You get a lot of support from family and friends	☐ 1
You get some support from family and friends	☐ 2
You get little support from family and friends	☐ 3
3. Assistance from organisations and the Government ***(Help from public, private or voluntary groups in terms of benefits, respite and practical information)***	
You get a lot of assistance from organisations and the Government	☐ 1
You get some assistance from organisations and the Government	☐ 2
You get little assistance from organisations and the Government	☐ 3
4. Fulfilment from caring ***(Positive feelings from providing care, which may come from: making the person you care for happy, maintaining their dignity, being appreciated, fulfilling your responsibility, gaining new skills or contributing to the care of the person you look after)***	
You mostly find caring fulfilling	☐ 1
You sometimes find caring fulfilling	☐ 2
You rarely find caring fulfilling	☐ 3
5. Control over the caring ***(Your ability to influence the overall care of the person you look after)***	
You are in control of most aspects of the caring	☐ 1
You are in control of some aspects of the caring	☐ 2
You are in control of few aspects of the caring	☐ 3
6. Getting on with the person you care for ***(Being able to talk with the person you look after, and discuss things without arguing)***	
You mostly get on with the person you care for	☐ 1
You sometimes get on with the person you care for	☐ 2
You rarely get on with the person you care for	☐ 3

Risk assessment tool

This document aims to:

- support healthcare professional decision making on whether a dyad should be approached to participate in the CARiAD trial
- monitor for risk occurences in dyads who are already participating.

For completion by:

- the healthcare professional responsible for approaching the dyad
- healthcare professionals involved in ongoing care

If the dyad fulfil the initial risk assessment and agree to take part in the study, this form should be kept in the handheld patient notes. Upon completion of the study a copy of the risk assessment should be returned to the study team.

If the answer to any of the statements is **NO**, the dyad are not suitable for inclusion in the CARiAD study and should not be approached to take part or should be withdrawn from the study.

If the dyad are to be withdrawn from the study or there are any concerns regarding dyad inclusion, please contact the CARiAD team.

CARiAD Trial Manager: Dr Jessica Roberts

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CARiAD Trial Administrator: Mrs Nic Nikolic

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	Yes/No	Yes/No	Yes/No	Yes/No
Patient and carer are aged 18 or over				
Patient has no known allergies to usually prescribed anticipatory medications				
Dyad are able and willing to access available healthcare support systems e.g. out of hours services				
Carer is not confused, disorientated or forgetful				
Carer has no significant vision problems				
Carer has sufficient literacy skills to understand and complete necessary documentation				
Carer has sufficient dexterity to prepare and give subcutaneous injections				
Carer is engaged with healthcare team, understands the importance of medications and is able to understand information relating to them				
No known relational issues between carer and patient which may contraindicate carer administration of medications				
No known issues of substance misuse in immediate circle of family and/or friends				
There is a suitable place for medications to be stored				
Date				
Print name				
Signed				

d. Appendix 4 – Caring Safely at Home materials

Background

The Brisbane South Palliative Care Collaborative developed a suite of resources known as the 'Caring Safely at Home' (CSAH) package. This package included educational resources and a Standardized Educational Framework. The resources enhanced lay carer confidence and capacity to assist palliative care patients to remain at home, with timely access to SC medication to control problematic symptoms as they emerge. The Framework supported community registered nurses to deliver a consistent approach when educating lay carers to prepare, store and administer SC injections for palliative care patients as symptoms emerged.

Training Objectives

- To understand why a standardised approach to education for carers required to prepare and administer SC injections in the home is a good idea;
- To understand why the CSAH resources were developed; and
- To understand the registered nurses role in delivering education utilising the CSAH resources.

Rational for training programme

The following describes the components of the standardised educational framework and the resources developed to support lay carers in their administration of SC medications. It is recognised that any educational package delivered by registered nurses to lay carers needs to be flexible. The framework must be able to be tailored to the differing geographical environments and jurisdictional requirements of individual health care services. However, to ensure consistent information is provided to lay carers certain core components of the framework need to be standardised.

The following list includes five component of the Standardised Educational Framework considered essential for teaching lay carers to deliver SC medications.

In the one-on-one education session, the RNs should:

1. **Teach and demonstrate to lay carers how to prepare and administer SC injections.** It is well recognised that palliative patients are inherently unstable and require timely access to palliative medications as soon as symptoms emerge. Consequently, lay carers should be taught the skills necessary to prepare and administer a SC injection. It is expected that every nurse will teach injecting skills according to their own educational style. Irrespective of style, the content taught should include all aspects of the 'Preparing and Giving a Subcutaneous Injection using the 10 Step Plan'.
2. **Explain the value of a blunt needle or needle-less technique.** To maximise patient/lay carer and staff safety and reduce the incidence of needle stick injury, it is considered best-practice to use a blunt needle or a needle-less technique when administering SC injections.
3. **Explain the rationale for the insertion of a second intima.** On occasion, a SC intima can become blocked. The insertion of a second intima ensures that the patient can still have timely access to symptom control medications, even when a nurse is not immediately available to change the intima.
4. **Explain the need to flush the static cannula with 0.3-0.5mls normal saline after SC injection(s) given.** Some SC medication doses are delivered in very small volumes; therefore flushing the cannula after the last injection ensures the palliative patient receives the complete dose of prescribed medications.

5. **Assess that the carer is competent to safely prepare and administer SC injections.** RNs have a legal obligation to ensure that a lay carer taught to prepare and administer a SC injection(s) is competent to do so. Competency can be demonstrated in the use of the competency checklist.

The resources developed by the CSAH project have been separated into mandatory and non-mandatory categories. The resources can be delivered at the discretion of the RN and lay carer. It is not expected that every lay carer will use all of the resources; a range of resources was developed to accommodate differing adult learning styles.

Mandatory Resources

All the **mandatory resources** should be introduced by the RN in the one-on-one educational session as outlined below:

- **Illustrated step-by-step charts** that provide a simple guide for lay carers to follow, when required to prepare and administer SC injections.
- A practice **demonstration injecting device** that includes a cannula inserted into stoma-type adhesive dressing that mimics a person's skin and other equipment involved with SC injections. This tool is useful for both the RN and the lay carer. The RN can use the kit as a teaching aid during education sessions and the lay carer as a practice kit after they have had the education.
- **Colour-**coding **medication labels** for labelling prepared syringes. This allowed lay carers to easily distinguish between the different SC medications with the aim of reducing carer stress and incidence of medication error. Labels must remain clear and legible. All injectable medications drawn up in syringes should be labelled IMMEDIATELY. The label is to be placed parallel to the long axis of the syringe and from the needle end of the syringe to the plunger. Ensure the label is flat when attached to the syringe, so it does not interfere with the barrel clamp or obscure the measurement gradient.
- A **colour-coded guide for medication (fridge magnet)** consistent with the syringe label colour-coding system, allows the lay carer to match relevant medications with symptoms, ensuring the right medication is given for the right symptom.
- A caregiver **daily medication diary** that allows laycarers to document aspects of medication administration. This allows the registered nurse and/or general practitioner to monitor the daily progress of symptom management.
- A competency **checklist** administered by the RN at the completion of the one-on-one education session. This checklist provides the RN with a mechanism to confirm that competency has been reached by the lay carer to safely prepare and inject SC medications.

Non Mandatory Resources

- A medication **booklet** 'Subcutaneous Medications and Palliative Care: A guide for caregivers', covering topics such as frequently asked questions, importance of symptom control; management of common palliative symptoms; commonly used SC medications and injecting processes.
- A **DVD** 'Palliative Subcutaneous Medication Administration: A guide for carers', demonstrating aspects of SC medication preparation and administration, safe storage and disposal of medications and includes a troubleshooting guide.
- Additional **illustrated step-by-step charts,** provides a simple guide for laycarers to follow when required to prepare and administer SC injections.

Additional Resources for the RN

- A lanyard**,** provides easy reference to the colour-coding medication legend as well as the principles of the standardised education framework.
- A **'RN** Medication **Classification Colour-Coded Legend'** poster has also been developed which outlines the symptoms, drug classifications, examples and colour-coded legend.

http://www.caresearch.com.au/caresearch/tabid/2145/Default.aspx

e. Appendix 5 – Authorisation of participating sites

Required documentation

Prior to initiating a participating site, we require:

- CVs of the research team
- Evidence that the structure of primary care and palliative care services are suitable for trial purposes
- Evidence of support of the local research network
- Evidence of arrangements for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research

Procedure for initiating/opening a new site

It is unlikely that we will need more than the 3 sites which has already confirmed participation. However, two additional sites have already expressed interest to join a future main trial, and we will likely draw on that interest if another site is needed to complete the pilot trial.

A new site will have local clinicians interested in testing the concept of lay carer role-extension to include administering as-needed SC medication to home-based dying patients ('champions'), and show equipoise. They will have an identified PI, SPC nurses/DNs willing to be trained in trial procedures and local research network support and.

Principal Investigator responsibilities

We expect the following from PIs:

- their attendance at the alternate month TMG meetings,
- training of new members of the trial team in the protocol and its procedures,
- ensuring that the ISF is accurately maintained,
- dissemination of important safety or trial related information to all stakeholders within their site,
- safety reporting within the agreed timelines