Full title of project

Accessing medicines at end-of-life: a multi-stakeholder, mixed method evaluation of service provision.

Short title / acronym

ACcess **T**o **MED**icines study / ACT MED

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Department of Health disclaimer
The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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List of abbreviations

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AR	Alison Richardson
CRN	Clinical Research Network
CST	Core Study Team
DM	David Meads
EoL	End-of-Life
HRQoL	Health Related Quality of Life
LR	Lesley Robertson
MB	Mike Bennett
MS	Miriam Santer
NC	Natasha Campling
PPI	Patient and Public Involvement
QoL	Quality of Life
RF-L	Research Fellow-Leeds
SL	Sue Latter
SRF-S	Senior Research Fellow-Southampton
SSC	Study Scientific Committee

Summary of Research

Background: Patient / carer access to medicines at end-of-life (EoL) is critical for control of symptoms, including pain and distress and recent evidence confirms end-of-life medicines optimisation is a research priority for patients and carers (1, 2). Anecdotal data from our recent studies (3, 4) suggests the prescription, dispensing, supply and associated information given about medicines (medicines access) is experienced by patients as often difficult, complex, demanding, lacking co-ordination and involves a multiplicity of professionals and services. Some of these problems were associated with GPs', who are main providers of EoL care delivery. Nurses often also take a lead role in providing community-based EoL care, but evidence suggests that here too there might be problems: prescribing by palliative care nurses has not been exploited to its full potential (5) and nurses find it difficult to access GPs for EoL prescriptions (6). Moreover, community pharmacists' expertise in palliative care medicines optimisation remains under-developed (7, 8). Furthermore, whilst there are promising innovations in EoL service delivery, little is known about the impact of these on patient access to medicines, and their cost effectiveness remains largely un-evaluated. We will investigate these issues and draw together findings to provide a comprehensive, critical evaluation of current practice, highlighting best practice, challenges and generating expert-informed solutions.

Aim: To provide an evaluation of patient and carer access to medicines at EoL within the context of current models of service delivery.

Design and methods: The study employs a number of distinct, related phases. Phase 1: Systematic review of research evaluating medicines access experiences, influences and outcomes within EoL service delivery models. Phase 2: On-line questionnaire surveys of GPs, nurses and pharmacists providing community-based EoL care: GPs (n≥200), community-based clinical nurse specialists (n≥200), community nurses (n≥200) and community pharmacists (n≥200) to identify current practices in facilitating EoL medicines access, barriers and facilitators to improving access, and identification of models of service provision for Phase 3 evaluation. Data analysis will use descriptive and inferential statistics. Phase 3: Evaluative case studies (n=4) of medicines access experiences within different service delivery models. The unit of analysis will be the service delivery model. Within each case, mixed methods will include 10 patient / carer medicines access logs and interviews (study entry and at 4 and 8 weeks), case note review of 40 patient records, health care professional interviews, and an economic evaluation. Logs will be analysed using descriptive statistics and visual display techniques. Patient / carer interview data will be audio-recorded, fully transcribed and analysed using Framework Analysis (9). Health care professional interviews will be audio-recorded, fully transcribed and analysed using Framework Analysis (9). Annotated time-lines will be constructed from patient records for each patient with decisions, action points, services used, information accessed, to understand medicines access processes and identify points that would benefit from action (10). From patient records, we will identify the main pathways and healthcare resources used therein, and use sources e.g. NHS Reference costs and the Personal Social Services Research Unit cost report to cost these pathways. Method and data source triangulation will be undertaken within each case and cross-case comparison will be used for theory-building. Phase 4: Telephone interviews will be conducted with 20-30 community pharmacists, and a national sample of key pharmaceutical wholesaler distribution companies (n=10) to illuminate the supply chain and barriers and facilitators to the effective supply of EoL medicines to patients and carers. Data will be analysed using Framework Analysis (9). Phase 5: An expert consensus-building workshop, to critically review and refine the study's preliminary findings and recommendations. Sample participants will be EoL experts (n=40) including national policy leads (for service & workforce development),

commissioners, EoL regional leads, patients, carers and health care professionals. With the study team, experts will generate policy, service delivery, practice and future research recommendations based on identification of: a) features of service delivery models that facilitate optimum access to medicines at EoL b) the mechanisms required to lever change and embed best models in routine practice.

Study endpoints: identification of gaps in service provision and deficits in care experienced by patients and carers, as well as models of good practice and the context that supports and embeds these into EoL service delivery. The research will identify critical points for service intervention and workforce development to improve patient access to medicines at EoL.

Background and Rationale

Patient / carer access to medicines at end-of-life (EoL) is critical for control of symptoms, including pain and distress and recent evidence confirms medicines optimisation at EoL is a priority for patients and carers (1). Anecdotal data from our recent studies suggests that prescription, dispensing, supply and associated information given about medicines (medicines access[1]) are experienced by patients as often difficult, complex, demanding, lacking co-ordination, and involve a multiplicity of professionals (3, 4). In one of the only few related studies we found in our initial literature scoping as part of bid preparation, US patients either experienced barriers to accessing medicines, resulting in insufficient medication and delays in pain relief, or, 'diligent pain management efforts by multiple clinicians in multiple settings resulted in an oversupply of pain medications for some patients and raised issues related to communication, coordination, and safety' (11). In a small study (6) in Ireland of 22 palliative care patients' access to medicines in the community, multiple points of system failure were found, including: patients unable to attend the GP surgery for a prescription, community nurse inability to contact GP for a prescription, carers' inability to collect prescriptions and / or medications from pharmacy and lack of appropriate pharmacy stocks. Our PPI participants told us about nurses collecting prescriptions from pharmacies for them, and we have also found that community nurses expend much effort in ensuring caseload patients access medicines by collecting prescriptions from GP practices and delivering them to patients (12). Applicants' (AB MB) review of UK cancer registry and primary care patient data (13) further highlights EoL patients' lack of access to opioids and that this is strongly associated with hospital death. The authors conclude that 'to date no UK research has systematically charted and evaluated patient experience of medicines access during the last year of life.'

Internationally, research also repeatedly highlights patients' and carers' needs for information about medicines in the EoL context (14, 15) and our recent systematic review evaluating educational interventions to help carers manage medicines on behalf of patients in the home highlighted that solutions remain elusive (2). Our recent studies (3, 4, 16) have focused on developing and testing education-focused interventions for pain and related medicines management in the home. Yet our experience in these studies suggested that the information patients and carers receive about medicines at a key point earlier in the patient pathway – i.e. when medicines are prescribed, dispensed and supplied to them – has a critical influence on their ability to self-manage medicines in the home. In the UK context, little is known about this important aspect of patient and carer experience.

At the same time as evidence suggestive of patient and carer access problems with traditional systems, including GP care delivery, little is known about this from the perspective of health care professionals. Additionally, there are indications that sectors of the workforce critical to EoL prescribing, dispensing, supply and early information-giving are currently under-utilised. While community-based clinical nurse specialists often take a lead role in care co-ordination at EoL (17),

[1] We define 'access' as patient and / or carer ability to obtain medicines from a prescriber and a dispenser together with any information and skills about medicines given at that point.

data suggest prescribing by palliative care nurses has not been exploited to its full potential (5). In addition, community pharmacists' expertise in palliative care medicines optimisation has been found to be under-developed (7, 8). Little is known about why nurses' and pharmacists' roles in this area remain under-utilised and evidence about its impact on patient experience of access to medicines is lacking. The recent NIHR (18) themed review of EoL care research highlighted the need for innovative models of care. Whilst there are some promising innovations in EoL care, such as pharmacist-attached palliative care teams, out-of-hours schemes, and community pharmacy palliative care access services, the impact of these on patient access to medicines, as well as their cost-effectiveness comparative to more traditional delivery models, remains largely un-evaluated. Our recent research (3, 4) also suggests that the supply chain 'upstream' may be a contributing factor to the complexity and problems with access experienced by patients. For example, patients and carers report a disconnect between prescriber choice of medicine/formulation/strength and pharmacy stocks, with prescriptions written without knowledge of currently available stock. Even where a patient's regular pharmacy made efforts to ensure stocks of a patient's 'usual' medicine, rapid changes during EoL care may lead to newly-prescribed medicines not being stocked. For medicines not in stock at the time the prescription is presented, the impact of medicines wholesaler opening hours and delivery times out of hours may block timely patient access. Applicant's (NC) previous research (19) with wholesalers and distributors into the supply chain of medical products to patients concluded that 'The consequences of supply disconnection revealed haphazard supply, unmet user needs and lack of information transfer between player groups' – including lack of patient feedback to wholesalers and distributors on the impact of their practices on patient access. However, to our knowledge, the community pharmacist, wholesaler and distributor perspective on the supply chain of EoL medicines has not been investigated to date. This therefore now needs examination in order to understand the contribution it makes to service delivery and the patient experience of medicines access in this context.
The proposal has developed from applicants' (SL, AR, MB, NC, AB, DM) collaborative research on Cancer Carers Medicines Management funded by Dimbleby / Marie Curie (3) testing educational support for family carers to manage opioid medicines on behalf of patients and HTA-funded SMART feasibility trial (4), focused on supporting patient self-management of analgesia and related treatments. It is also informed by experiences of applicants' (MB, AB, DM) on-going trial of a homebased supportive intervention for self-management and monitoring of analgesia at EoL in PGfAR funded IMPACCT (16). These studies focus on supporting self-management of medicines in the home e.g. self-administering medicines and monitoring and recording medicines administration and symptom control. Experiences from these studies suggest that a key influence on patient / carer medicines management, symptom control and subsequent unplanned use of out-of hours services occurred earlier / elsewhere in the patient pathway, i.e. when prescriptions are prescribed, dispensed and supplied. Patients and carers told us anecdotally that these, and the information support received at this point, were crucial to achieving good symptom management at EoL, yet their experiences were problematic. We propose therefore to systematically study this experience of access in more detail, addressing the question: what are stakeholder experiences of EoL medicines access services and the characteristics of service provision that can support quality service delivery? We will rigorously compare experiences across different service models in order to understand features that define good or poor quality medicines access for patients.

To our knowledge, no research has systemically studied patient experience of medicines access against the backdrop of differing features of service delivery – such as GP-led care, consultant-led care, or hospice-based specialist nurse team-led care - currently operating in England and / or the perspectives of health care professionals and pharmaceutical wholesalers and distributors involved in medicines prescription, dispensing, supply and information-giving processes. Our study will complement Pollock et al's NIHR funded research (20), describing the management of, and information and training needed for, EoL medicines administration in the home setting.

Current national policy on EoL care has framed this proposal: the study will examine a key issue (access to medicines) that exemplifies current concerns and imperatives – variation in service delivery and choice of care (21), as well as the principles outlined in Ambitions for End of Life Care (22) national action framework – fair access to services, maximising comfort and well-being, and coordination of care. The research will also contribute to understanding the effectiveness of recent recommendations for EoL service delivery (22), by incorporating evaluation of models of care delivery that include case co-ordination, shared records and 24/7 cover and other distinctive features.

A series of key reports have stressed the pressing need to improve EoL services due to unacceptable variation in access to and experience of care (21 22). NIHR research (19) has also identified poorly coordinated services and limited access to specialist palliative care. Our recent research (3, 4) suggests that good access to, and information about, medicines at EoL remains a variable and often burdensome experience for many, affecting symptom control, quality of life and use of unplanned and out-of-hours services. At the same time there are gaps in our knowledge about health care professionals' views on this, and why potential workforce solutions (nurses and pharmacists) to improving medicines access are apparently under-utilised. Zeigler et al's small survey (5) found there is potential to improve nurse prescribing in palliative care and recommended further research into patients' views of palliative care non- medical prescribing. Savage et al (7) highlighted significant scope for improving access to and interaction with, community pharmacists by people with cancer pain and their families. The number of nurse and pharmacist prescribers is rising, with over 30,000 nurses (23) and 3,845 pharmacists (24) now trained as independent prescribers. In addition, there are significant changes to community pharmacy services as the national integration agenda is driven forward: e.g. commissioning of palliative care medicines access services; higher use of summary care record by community pharmacies; and community pharmacy integrated urgent/emergency care services. There are also other innovative models of EoL service provision emerging which offer the potential to improve medicines access experiences, but to date their impact on this important aspect of patient experience and their cost effectiveness remains largely unexplored. At a time when EoL care is a national service delivery and research priority, there is therefore an urgent need to provide a systematic and detailed evaluation of these issues in the current national context to inform policy, service delivery and organisation, research and practice going forward.

Aims and objectives

Aim: To provide an evaluation of patient and carer access to medicines at end-of-life within the context of models of service delivery.

Objectives:

1. To produce a critical overview of existing research on experiences and outcomes of medicines access within EoL models of service delivery, through a systematic literature review (Phase 1).
2. To undertake a large scale survey to evaluate EoL care professionals' current practices, identify factors influencing professionals' contributions, the potential of the community-based nurse and pharmacist workforce to improve patient access to medicines at EoL, and provide an overview of current models of service delivery (Phase 2)
3. To evaluate and compare patient and carer experience of medicines access within models of EoL service delivery, including those featuring innovations in care, and to investigate their integration and sustainability through undertaking mixed methods case studies of practice (Phase 3)
4. To estimate the cost-effectiveness of service models (Phase 3)
5. To map patient 'access to medicines pathways' at EoL, including time-lines of problems, decisions, actions and use of services (Phase 3)

6. To identify barriers and facilitators to maximising the contribution of the nurse and pharmacist workforce to medicines access at EoL (Phases 2 & 3)
7. To interview community pharmacists and wholesalers and distributors to evaluate supply chain processes and identify challenges in providing access to EoL medicines (Phase 4)
8. To convene an expert consensus-building workshop to review study findings and generate recommendations on key characteristics of EoL service delivery that result in responsive, person-centred, coordinated medicines access, together with identification of factors that will embed and sustain characteristics in routine practice (Phase 5)
9. To use the expert consensus workshop to identify models to evaluate in a follow on study, comparing the effectiveness and cost-effectiveness of service delivery models (Phase 5)

Study endpoints are designed to identify gaps and deficits in service provision experienced by patients and carers, as well as highlight models of good practice and the context that supports and embeds these into EoL service delivery. The research will identify critical points for service intervention and workforce development to improve patient access to medicines at EoL. We will build our recommendations on the findings from our comparative evaluation of medicines access experiences within service delivery models - including new and innovative service delivery characteristics - and through stakeholder engagement in the consensus workshop (Phase 5). The research will provide a robust evidence base to underpin recommendations on service delivery models and workforce development for best medicines access services for patients and carers at EoL.

Design and theoretical/conceptual framework

The study uses a multiphase mixed methods design (25) with sequential, linked phases, where initial phases inform subsequent phases (see Study Flowchart). The study will draw on systems thinking to understand the issue of accessing medicines at EoL in the health care system. This perspective acknowledges complexity and recognises the multiplicity of actors, the ever-changing context and that systems interact over time to create new patterns (26). It recognises the importance of multiple stakeholder perspectives and an 'inclusive set of health system stakeholders is critical to designing more robust interventions and their evaluations'. (p52 26) We intend that by mapping out a conceptual pathway of dynamic sub-system interactions in this study, we will then be in a position to help forecast how any newly constructed interventions that we intend to evaluate in a follow on study will stimulate changes in the health care system. And as de Savigny and Adam (27) suggest, 'interventions may be re-designed to bundle in additional elements amplifying previously unappreciated synergies and mitigating potentially negative effects' (p52). A whole systems approach will frame our consideration of medicines access during study data collection and analysis. A whole systems approach is characterised as one in which: services are responsive to the needs of the individual patient/ carer, all stakeholders accept their inter-dependency and that the action of any one of them may have an impact on the whole system, those using the system do not experience gaps or duplication in provision and where relationships and partnerships are enhanced (28). Such an approach is critical to improving public access to health services (29).
The study will also use logic models to help characterise the problems with, and interventions for improving, medicines access within different service delivery models. A logic model is a summary diagram that maps out an intervention and conjectured links between the intervention and anticipated outcomes in order to develop a summarised theory of how a complex intervention works (30). Logic models will be used to map mechanisms of action of interventions, as well as to chart moderating and mediating factors that lead to intended short and long-term outcomes and broader impact. We will build on our recent and on-going research studies (3, 4, 16) as well as the systematic literature review in Phase 1, and data from our surveys in Phase 2 to develop a logic model / framework analysis of what we think happens in service delivery models and use this as a

basis for exploring certain high impact areas in Phase 3. Logic models will be further populated with data from community pharmacists and pharmaceutical wholesalers and distributors in Phase 4 and final versions will be used to inform the Phase 5 multi-stakeholder workshop. Through charting medicines access interventions, understanding their impact and outcomes, mediating factors and the theoretical mechanisms of action of interventions, logic models will also inform the design of a follow on study to evaluate and compare intervention's (service model's) impact on patient and cost outcomes.

Research plan / Methods (Please see Appendix 3 study flow chart)

Phase 1: (Objective 1): A systematic review of research evaluating medicines access experiences, influences and outcomes across a range of different EoL service delivery models.

We will build on our initial scoping of literature conducted as part of proposal development and systematically search for and review international research studies for existing evidence of: a) patient and carer experience of medicines access within the context of different models of service delivery b) patient and carer outcomes associated with medicines access experiences. We will search key electronic bibliographic databases Medline, CINAHL, PsycINFO using MeSH and other recognised search terms and Boolean operators e.g. terminal care AND medicine* AND access. We will also search databases of systematic reviews including the Cochrane review database and identify relevant research in progress through trial registries such as ISRCTN and on-going systematic reviews through e.g. PROSPERO. Grey literature will be systematically searched using HMIC and EAGLE.

Our initial literature scoping suggests only a limited number of research studies in this area, so at this stage we consider it unlikely the review will exclude studies on the basis of study design or quality.

We will assess study quality as part of the review using recognised tools appropriate to the study design e.g. CASP checklists, GRADE assessment of systematic reviews and quantitative studies. Quality appraisal will be undertaken by two members of the research team (SRFs). Following systematic quality appraisal, we will produce a narrative synthesis (31) of the literature. The review will summarise and highlight key issues and gaps for further investigation in Phases 2, 3 and 4 of the study.

Phase 2: (Objectives 2, 6): On-line questionnaire surveys of GPs, community-based nurses and pharmacists practising in EoL care contexts.

Sampling:

We will survey GPs, community-based palliative care clinical nurse specialists, community nurses and community pharmacists. These represent the predominant groups of health care professionals in the community-based workforce with potential to influence patient / carer experience of EoL medicines access. Data will be collected on current medicines access-related practices, the impact this has on patients and factors facilitating and inhibiting professionals' ability to improve access, including (for those without a prescribing qualification) prescribing for EoL patients. We will also collect data on models of service delivery in operation, and this will inform Phase 3 sampling.

We will aim for a sample of at least 200 in each professional group, and we will assume a 30% response rate for all professional groups.

GPs: We will survey GPs via a link to the on-line survey sent to GP practices in 4 Clinical Research Network (CRN) areas: 2 CRNs in the south of England and 2 CRNs in the north. CRN primary care leads will identify research active (Research Sites Initiative (RSI)) practices for our sample of practices. Practices will then be e mailed a link to the survey. We anticipate that this will result in the survey link reaching at least 667 GPs, to achieve a sample of at least 200 with a response rate @ 30%.

Clinical nurse specialists: We will survey the population of community-based palliative care clinical nurse specialists via a link to the on-line survey distributed to nurse leads in all hospices listed in the

Hospice UK directory serving adult populations in England (n=approximately 180). Community clinical nurse specialist teams outwith hospices will be identified by a telephone call / e mail to hospice nurse leads by the researchers and a survey link distributed to lead nurses for these community teams. We will ask all nurse leads to cascade this link out to the nurses in their teams. We anticipate the total number of palliative care clinical nurse specialist teams to be approximately 250, with an average of 5 nurses per team. Our recent studies (3 4) and scoping work as part of this proposal suggests there is considerable variation in the proportion of nurse specialists prescribing in a team, but that we can estimate an average of 2-3 nurse prescribers per team. We therefore estimate that the survey link will reach approximately 1250 community specialist nurses, including 625 nurse independent prescribers.

Community nurses: Recent data indicate that there are 8023 nurses working as district nurses, staff nurses or community matrons in England, of which there are approximately 1123 (14%) with an independent prescribing qualification (32). We will distribute the on-line survey link through a sample of 2 of the 17 NHS and Foundation trusts employing community nurses (one southern England and one northern trust) to target approximately 1000 of the community nursing workforce. We expect this to reach approximately 140 independent prescribers. With an estimated response rate of 30%, we will achieve a sample of > 200 nurses participating in the survey and at least 42 nurses with an independent prescribing qualification. The survey link will be distributed to nurses via a local collaborator / service lead identified by local CRNs e.g. non-medical prescribing leads or Director of Nursing in each trust. Costing for local collaborator / service lead time for this has been included.

Pharmacists: Pharmacists with a prescribing qualification are increasingly deployed in GP practices, with 400 new clinical pharmacist places already established set to grow to 1500 in the next few years (33). Recent data (34) indicate approximately 547 (30%) pharmacist prescribers prescribe in primary care settings and 237 (13%) in community pharmacy. We will identify the sample of pharmacists working in GP practices and community pharmacy via primary care leads in all 15 CRNs contacting research active (Research Sites Initiatives) GP practices and community pharmacies, and also via our existing contacts within the Primary Care Pharmacy Association and the Palliative Care Pharmacist Network. We anticipate this will enable us to reach sufficient community pharmacists to give a final sample, with an estimated 30% response rate, of at least 200. Palliative care and prescriber networks and interest groups e.g. Association for Prescribers will also be used to recruit the sample.

Data collection: Key issues identified from Phase 1 systematic literature review, as well as our recent studies (3, 4) and PPI liaison will be used to inform questionnaire design. Selected items in questionnaires used successfully in previous national surveys (35, 36) of non-medical prescribers by applicants SL & AB will be incorporated into the design, adapted to the EoL context. The questionnaire will be designed with response options to collect data from both prescriber and non-prescriber nurses and pharmacists for ease of distribution and administration. We will seek data on such issues as: the extent / comprehensiveness of professionals' prescribing, dispensing and information-giving for EoL patients; problems, challenges and facilitators in providing access to EoL medicines for patients and reasons for this; nurses' and pharmacists' reasons for not training as a prescriber; education, training, support and contextual factors needed to deliver more responsive, patient-centred, co-ordinated services to facilitate EoL medicines access. Data will also be sought from each participant about the type of EoL service model they operate in and engagement with key policy and practice features of service delivery, critical for developing and sustaining new models of care: e.g. engagement in care co-ordinator roles, provision of 24/7 care access and out-of-hours prescribing. See Table 1 for examples of questionnaire data collection. Respondents will be asked to indicate if they are willing in principle to participate in Phase 3.

Study objective	Example data to be collected in Phase 2 questionnaire
To evaluate EoL care professionals' current practices (Objective 2)	• Access routes provided to patients for prescriptions e.g. telephone consultations, home visits, electronic repeat prescription requests • Access routes followed by non-prescribing nurses and pharmacists – what routes are used to initiate prescriptions? • Typical time taken from patient request for medicines to patient receipt of medicines • What is the out-of-hours provision for patients needing to access EoL medicines? • What information is typically provided to patients / carers at the point of prescription and / or supply? How comprehensive is this? How frequently is it offered? • Views on the quality, safety and impact on patients of respondent's current EoL medicines access service provision e.g. What proportion of EoL patients on practitioners' caseload experience poor or good access in the current model of service provision? • What are perceived gaps in service provision? How might these be addressed?
To Identify factors influencing professionals' contributions (Objective 2) To identify barriers and facilitators to maximising the contribution of the nurse and pharmacist workforce to medicines access at EoL (Objective 6)	• What factors support examples of good practice? • What are the limiting factors or challenges to providing good or better patient access to EoL medicines? • What are the reasons for non-prescribing nurses and pharmacists choosing not to train as prescribers? • What contexts, structures or mechanisms are associated with these facilitators and inhibitors of practice? • What is required to address these factors to support integration and sustainability of good access services for all? • What education, training, support and contextual factors are needed to support nurses, pharmacists and doctors to deliver more responsive, patient-centred, co-ordinated services to facilitate EoL medicines access?

To evaluate the potential of the community-based nurse and pharmacist workforce to improve patient access to medicines at EoL (Objective 2)	
To provide an overview of current models of service delivery (Objective 2)	• Respondents will be asked to summarise the model of service delivery in which they are employed e.g. GP with / without practice-based pharmacist; specialist nurse team working from a hospice with / without nurse prescribers; pharmacist providing palliative care medicines access service • Respondents will be asked about engagement with key policy and practice initiatives e.g. shared records, care co-ordinator roles, provision of 24/7 care access and out-of-hours prescribing.

Table 1: Phase 2 questionnaire design mapped to study objectives

We will keep the questionnaire brief (< 10 minutes to complete), using predominantly closed questions and structured response options, and in on-line format using Survey Monkey® to increase response rates. Paper copies of questionnaires will also be made available if preferred by respondents, together with stamped addressed return envelopes. To maximise response rates, we will send a follow up e mail two weeks after first distribution, a second follow up one week later and a third and final follow up one week later. If response rates are low e.g. less than 50 GPs (equating to a 7.5% response rate), we would consider increasing the number of CRNs through which we distribute the survey link. We would also seek opportunities to attend relevant health care professional national conferences for completion of questionnaires. If response rates remained poor, we would consider achieving objectives 2 and 6 through interviews with relevant groups of GPs, community specialist nurses, community nurses, and pharmacists with strategic oversight of the issues e.g. interviewing Macmillan GP Advisors.

Analysis: Analyses will be conducted using Stata, with reporting of results following the appropriate STROBE guidelines. The final analysis plan will be confirmed prior to the end of the data collection period in agreement with the Study Advisory Group. The focus of the analysis will be descriptive, presenting results as frequencies and percentages, or means and medians with corresponding measures of spread. Necessarily, analysis will be based on completed responses to each question. We will present point estimates with confidence intervals (CIs) to indicate precision, but interpretation of all results will acknowledge possible biases arising from the nature of the sampling (we cannot be certain all those intended to receive the questionnaire did) and non-response to the questionnaire. We will focus on interpreting absolute figures, assuming that the most common responses at least broadly reflect the population.

Questionnaire responses and missing data will be summarised by group (specialist and community nurses, pharmacists and GPs). Comparisons between groups will be presented as absolute differences (e.g., difference in means, difference in proportions) with associated 95% confidence intervals. Responses from those working as part of the same team will be grouped in order to help define the service delivery models.

Sample size: A target of at least 200 per group was set based on estimating proportions to within a desired level of precision. A sample of size 200 will ensure 95% confidence intervals are no wider than +/-7% (based on intervals calculated using the normal approximation).

Phase 3: (Objectives 3, 4, 5, 6): We will conduct in-depth, contextual evaluation of medicines access experiences, service costs and outcomes in different EoL service delivery models, drawing on multiple stakeholder perspectives within multiple embedded, mixed method case studies (n=4). We will then undertake a cross-case comparison of medicines access experiences, and conduct an economic evaluation of these vs. standard care.

Sampling of case sites:

Case studies are concerned with analytic or theoretical generalisability rather than statistical generalisability (37). We will purposively select 4 service delivery models across England, using a sampling frame derived from Phase 2 respondent EoL service models and informed by logic models (see above). We will stratify Phase 2 responses according to type of service model and geographical location. We may also supplement this Phase 3 case site sampling strategy through using knowledge that the CRNs hold regarding GP practice characteristics. Sampling will
ensure a range of service delivery models are included, and will cover both i) typical models of service delivery (e.g. consultant-led specialist palliative care) and (ii) models of service delivery that include innovative characteristics outlined in national choice offer care models: 24/7 community care, shared records, named responsible clinician and case co-ordinator model sites (22). The case study unit of analysis will be the service delivery model (e.g. a hospice-based nurse specialist team as the dominant mode of care provided to the patient and carer).

Sampling, data collection and analysis of sub-units:

The sample size is in line with the principle of analytical rather than statistical generalisability as above and is based on a requirement to achieve data saturation within the case (interviews) and to pattern match (37) data in the logs and the patient case records. Internal generalisability (38) within each case will be maximised by sampling 10 patients / carers participating in logs and interviews and 40 case records that are representative of others in the case.

The unit of analysis is the service delivery model, with embedded sub-units of analysis:

a) Prospective data from 10 patients (and their carers where appropriate), sampled within each case using maximum variation sampling e.g. we will include patients with non-malignant life-limiting illness, and patients with a range of primary cancer sites. Inclusion criteria will be patients no longer receiving curative treatment, in receipt of prescribed medicines for symptom management, likely survival anticipated to be no less than 8 weeks, in receipt of service delivery typical of the case site focus, able to speak and write English and able to give capacity to consent to take part in the research. Sampling will be dependent on service delivery model, but is likely to focus on Gold Standard Framework registers, out-patient palliative care clinics, hospice referrals and specialist and community nurse caseloads. Patients and carers will be recruited by opportunistic screening of the above sources by research nurses. They will be sent a letter of invitation, with subsequent consent taken by the research nurse or Senior Research Fellow. Based on applicants' recent studies (3 4), we estimate an acceptance rate of approximately 50%; therefore 20 patients per site will need to be approached to reach our recruitment target of 10 patients per case study site. Patients will be recruited by research nurses at the site (costing included). Patients / carers will be asked to complete a structured log on medicines access experiences over an 8 week period from recruitment into the study. Collecting data over an 8 week period is likely to be feasible in relation to survival, whilst allowing for key issues to be studied e.g. two changes to / repeats of 30 day prescriptions. Logs will be sensitive to the EoL context and kept simple to minimise patient / carer burden. We expect that logs will in most instances be completed by patients and carers; our recent studies (3 4) have found that the tasks of medicines management are shared by patients and carers, with carers taking on more of this responsibility as disease progresses. Data will focus on patient / carer experience of obtaining prescriptions and medicines, plus supporting information, and will address

office and out-of-hours. Patients / carers will be asked to record new or repeat prescriptions, who was contacted, how, effort and time taken to receive prescription, any incorrect or duplicate medicines received, and to rate satisfaction with information about medicines given at each point of contact. Our recent studies indicate attrition rates in this population of between 21% (4) and 47% (3) over a similar period. We consider that minimum data required for meaningful analysis consists of study entry interview, 4 weeks log and week 4 interview. We will re-recruit to replace any patients / carers who withdraw prior to this point, resulting in a study entry, 4 weeks log and week 4 interview for 10 patients per site. Data analysis: Data from logs will be used to characterise features of medicine access and will be summarised using descriptive statistics and visual display techniques; data analysis will include both within-patient /carer participant over time to illuminate any changes in medicines access experiences and across patient / carer participants for pattern-matching within the case. This latter will include some aggregation of data to describe main features of access e.g. the numbers and types of health professionals issuing prescriptions to case study patients, the number of patients using out-of-hours services, and the number of times patients accessed out-of-hours services. Patients/ carers will take part in one face-to-face semi-structured interview on study entry to explore experiences of EoL medicines access to date, and further brief telephone interviews (4 and 8 weeks) about experiences, drawing on log data. Our recent studies (3, 4, 16) and PPI in bid preparation indicate high levels of patient and carer participation in interviews can be expected and that delivery at this level of frequency will be achievable. Interview data will be audio-recorded, fully transcribed and analysed using Framework Analysis (9).

b) We will purposively sample up to a maximum of 5 health care professionals (e.g. specialist nurse, GP, specialist palliative medicine doctor) who are the main providers of EoL care to each of the 10 patients in the case study service model and invite then to take part in a brief semi-structured interview. Health care professionals will be asked about their experiences of facilitating access to medicines for the case study patients, including barriers and facilitating factors. We will also seek views on factors that enable practice transformation and good practice with respect to medicines access to be sustained and embedded. Interviews will be audio-recorded, fully transcribed and analysed using Framework Analysis (9) to identify main themes.

c) A retrospective sample of 40 patient records (including patients taking part in logs and interviews) will be reviewed, to map medicines access patient pathways. Records will be accessed from GP practices and specialist palliative care provider sites that typify the service model being studied within the case study site. A purposive sample of patients listed on these practices' Gold Standard Framework register, and /or patients from hospice records and specialist nurse caseloads for a minimum of 8 weeks will be selected. Patients will be selected if they have been prescribed medicines for symptom management and are in receipt of service delivery typical of the case site focus. Data will be extracted on: medicines prescribed, when, by whom, duration, services used, including out-of-hours, unplanned or emergency services, hospice or hospital admissions and medicines information provided. Analysis: Annotated time-lines for each patient with decisions, action points, services used, information accessed, to understand medicines access processes and identify points that would benefit from action (10). This latter will include some aggregation of data across patients to describe main features of access e.g. the numbers and types of health professionals issuing prescriptions to case study patients, the number of patients using out-of-hours services, and the number of times patients accessed out-of-hours services. We will also identify the main pathways and healthcare resources used therein, and use sources e.g. NHS Reference costs and the Personal Social Services Research Unit cost report to cost these pathways (see below).

Case studies:

The unit of analysis (case) is the service delivery model:

- **Case 1: GP as main prescriber**
- **Case 2: Clinical Nurse Specialist non-medical prescribing team**
- **Case 3: Enhanced services for palliative care**
- **Case 4: 24/7 telephone support service**

with embedded sub-units of analysis:

- **Patient / carer logs and interviews, and patient case record analysis (Cases 1, 2 and 4)**
- **Healthcare professional interviews (Cases 1-4)**
- **Commissioner interviews (Case 3)**
- **Documentary analysis (Case 3)**
- **Economic analysis (Cases 1-4)**

We have analysed the literature from our systematic review (Phase 1), our Phase 2 survey data and discussed our findings with our SSC members. As a result, we believe that these four case studies represent the range of both typicality and innovation in current service delivery models of end of life care. Case 1: GP as main prescriber: this case represents a typical, well-established service where the patient's GP is the patient's main prescriber of palliative care (and other) medicines; the patient does not receive prescriptions from non-medical (nurse, pharmacist or paramedic) prescribers in this model of service delivery. Case 2: Clinical Nurse Specialist (CNS) non-medical prescribing team: here the focus of the case study is on an innovative model of service delivery where the provision of palliative care (and other) medicines provided to the patient includes a high level of prescribing by palliative care Clinical Nurse Specialists who are qualified independent prescribers. The prescribing Clinical Nurse Specialists provide medicines to patients as part of specialist palliative care and the CNS team are typically based at a local hospice. Case 3: enhanced services for palliative care: the case focuses on evaluating medicines access from community pharmacies that are commissioned to provide an enhanced service that may include stocks of core palliative care medicines, extended opening hours and service awareness-raising by the pharmacy to patients, carers and health care professionals. Although local enhanced pharmacy services for palliative care have been commissioned in some CCG areas / regions for a number of years, they represent an important innovation that is likely to influence medicines access, that to our knowledge, remains un-evaluated. Case 4: 24/7 telephone support service: this case focuses on a service delivered by nurses, providing 24/7 telephone advice to palliative care patients and carers, including advice on symptom control and other medicines-related issues. As well as providing out-of-hours care, the service is also characterised by access to shared electronic records and co-ordination of care. As such, it embodies several innovative characteristics of service delivery that are beginning to be introduced within some palliative care services more generally.

For one of the case studies only (Case 3) the methods of data collection will vary from those outlined above and will instead utilise: qualitative interviews across three sample groups, supplemented by documentary analysis (refer **to protocol page 18** and Appendix 2 for an overview and rationale for this protocol change).

Case 3

The service delivery model in this case is community pharmacy delivered enhanced services for palliative care (on demand availability of specialist drugs). According to national service level data from the Pharmaceutical Services Negotiating Committee updated in December 2018, there are 71

enhanced services for palliative care across England (46). These services are in the main commissioned by local Clinical Commissioning Groups (CCGs) or NHS England:

- 45 services are commissioned by the respective CCG(s). 6 services are commissioned by more than 1 CCG, and 3 CCGs commission 2 services each.
- 16 services in the following regions are commissioned regionally by NHS England; and 1 by an NHS area team, part of NHS England (17 in total):
    - South West - Bristol - N Somerset, Somerset, Swindon, S Gloucestershire,
    - W Midlands - Staffordshire + Shropshire
    - E Midlands - Derbyshire, Nottinghamshire, Northamptonshire
    - Greater London - Camden, Kensington + Chelsea
    - West Yorks - Bradford, Calderdale, Kirklees and Leeds
- For 8 services publicly available information on who commissions the service was not evident.
- 1 service is commissioned by a hospital Trust.

The services are funded to provide stocks of "core" lists of palliative care medicines (determined at the service level) and to provide community pharmacy extended hours of opening where possible. A key component of the service is promoting awareness of this service provision to both healthcare professionals and patients. There is very little research evaluating community pharmacy delivered enhanced services in general, and to the best of our knowledge no studies have evaluated palliative care specific enhanced services.

Case 3 - Methods of data collection

Sample groups

It is proposed that three sample groups will be approached to comprise the case study of this service:

1. Community pharmacists providing enhanced services for palliative care
2. Commissioners of enhanced services for palliative care
3. Community based healthcare professionals: palliative care clinical nurse specialists and community nurses who utilise enhanced services on behalf of patients/carers; community pharmacists (not providing enhanced services) + primary care pharmacists; and General Practitioners.

Sampling

Sampling strategies are outlined in relation to the three sample groups. Groups 1 and 2 will be unique to this case (sampled on a wider, national scale than the other cases) and group 3 will utilise community-based healthcare professionals interviewed within the context of the other case studies.

1. <u>Community pharmacists providing enhanced services for palliative care</u>

We will generate important new insights into enhanced pharmacy services for palliative care through capturing the views of pharmacists providing the service. 37 community pharmacists providing enhanced services for palliative care who participated in the Phase 2 survey, agreed to be contacted in relation to Phase 3 of the study (providing contact details). This sample includes a combination of community pharmacies that are both multiples and independent pharmacies: 9 multiples, 28 independents. There is geographical spread across England in the sample: 16 within Greater London, and 18 from elsewhere in England, representing approximately 15 Clinical Commissioning Group regions. We will therefore build on the positive response to our survey, purposively sampling this group of community pharmacists as part of a re-designed case study on

enhanced pharmacy services. In addition, as multiples / large chains are under-represented in our Phase 2 sample, we will use a key contact at the Company Chemists' Association who has agreed to distribute study information and invitations for pharmacists to take part through research leads in in their member organisations (Asda, Boots, Lloyds Pharmacy, Morrisons, Rowlands Pharmacy, Superdrug, Tesco and Well).

Snowball sampling will also be used, so that community pharmacists who participate in an interview will be asked if they can identify any other community pharmacists that provide such services. Based on a maximum estimated 40% response rate from Phase 2 respondents, and using these additional recruitment routes, we estimate we will conduct up to 20 interviews. If less than 20 interviews result, or saturation has not been achieved, sampling could be extended via CRNs in England who are active in community pharmacy research with a pharmacy lead or pharmacy champions.

Pharmacists will be asked to provide details of their service commissioners, and provide copies of service level agreement documents, to inform commissioner sampling (see below).

2. Commissioners of enhanced services for palliative care

Our scoping work indicates that it will be essential to capture commissioner views as part of the case study. For example, there is unexplained variation in financial recompense to pharmacies for the service, the range and level of methods of commissioner oversight and service review also appear to exhibit considerable variation. Both CCG and NHS England commissioners will be sampled, in order to identify and evaluate any differences in service provision, monitoring and review between local and regional level commissioning, and to investigate any resulting effects on access to medicines for patients and carers.

Snowball and purposive sampling via community pharmacists who are interviewed (sample group 1) will enable identification of a linked commissioner sample. Community pharmacists will be asked to provide commissioner and service details for their enhanced service. We will purposively sample to enable us to include both CCG and regional commissioning models; we will aim to link data from the pharmacist provider interview with the service commissioner interview, each to form embedded sub-units within this case study.

It is known from preliminary investigative work that Local Pharmaceutical Committees may be the delivery arm of NHS England commissioned enhanced services. Where this is relevant to the commissioner sample, linked interviews with the LPC representatives will additionally be sought.

In total, we will aim to interview at least one commissioner for each of the five regionally commissioned services, together with the LPC counterpart as appropriate (n=5-10), and 4-6 CCG commissioners, stopping data collection when data saturation is reached.

3. Community based healthcare professionals

Nested sampling will occur with healthcare professionals interviewed within Cases 1, 2 and 4 (refer to Appendix 2); specifically, community based healthcare professionals, who will be asked for their views on enhanced service provision in their area as part of scheduled interviews in these sites. In-depth questioning regarding these services is most likely to occur with palliative care clinical nurse specialists and community nurses who may have experience of utilising enhanced services on behalf of patients/carers.

Community pharmacists (not providing enhanced services), primary care pharmacists, and general practitioners who are interviewed as part of Cases 1, 2 and 4 will be asked about their awareness of such services in their area, and where there is awareness they will be asked for their views on these services in aiding access to medicines.

Feasibility work has provided important contextual background to current enhanced service provision, including highlighting best methods for data collection as well as issues that warrant further systematic investigation in this case study. A key issue in relation to a potential case study focused on enhanced community pharmacy services for palliative care concerns our inability to link patients using specific pharmacies providing an enhanced service back to a small (2-3) number of GP practices for sample recruitment:

- **Patients using any one enhanced pharmacy service are likely to be registered with a large number of different GP practices – it is not feasible for the research team to negotiate access to and recruit from a large number of GP practices across a wide geographical area.**
- **Focusing on patients using an enhanced service who are registered with 2-3 identified GP practices would mean that recruiting sufficient patient numbers would be too challenging within the study timeframe.**

We have also concluded that there is no reliable way of identifying patients who use a particular local enhanced service from GP practices. We have checked out with a number of GPs that although patients may nominate a preferred pharmacy as part of the Electronic Prescribing Service (EPS), in practice this does not mean that a particular pharmacy will be used. For example, patients often don't consistently use the same pharmacy; lack of stocks may mean that they take the prescription round to wherever it can be filled. In addition, if an administration chart for use by community nurses is needed then a print copy of a prescription is used instead of an electronic one. Many of the palliative care patients we wish to recruit are likely to be prescribed Controlled Drugs (CDs). Prescribing of CDs via the EPS has only just being introduced, so it is likely that in practice CDs are still being prescribed using paper prescriptions, thus further confounding any reliable link between EPS and identified pharmacy use.

Additionally, difficulties likely to impede patient and pharmacist recruitment through community pharmacies are: lack of awareness by community pharmacists as to which of their patients are palliative; high levels of corporate chain pharmacy provision, with resulting uncertainty about corporate governance agreement to study participation; high pressures on community pharmacists' time due to workload; and general lack of familiarity with, and history of community pharmacy involvement in, research.

For the reasons outlined above, therefore it is not feasible to collect patient data in Case 3.

Data collection

Qualitative interviews and analysis

Semi-structured qualitative interviews will be performed via telephone for sample groups 1 and 2. For sample group 3, interviews will include either face to face or telephone and may occur in groups e.g. for palliative care clinical nurse specialists and community nurses, where opportunities are taken to add interviews to naturally-occurring meetings.

Interview data will be audio-recorded, fully transcribed and analysed using Framework Analysis (9).

Semi-structured interview guides will be used. Additional questions will be added to the existing healthcare professional interview guide for sample group 3, and for sample groups 1 + 2, interview guides will be developed that elicit community pharmacists' and commissioners' views on: aims/objectives and incentives for service provision; details regarding extra medicines stocked and / or extended opening hour provision; the level of information-giving regarding these services to patients/carers, and to health care professionals; liaison with other pharmacies if prescriptions

cannot be filled; levels of coordination with prescribers; service delivery/audit requirements; training requirements to deliver the service; liaison with local palliative care teams; frequency of review of the formulary listed medicines; perceived effectiveness of the commissioning process; perceived impact (or otherwise) of the service in meeting the needs of patients/carers; whether service provision enhances out-of-hours access; whether stock levels are sufficient to meet local needs and variability in needs; levels of signposting to the service by other healthcare professionals; barriers and facilitators to service commissioning and delivery; and how service improvement is or can be promoted.

Interview guides for sample groups 1 + 2 will incorporate views on costs and resources to support service delivery, and the relative effectiveness of the service at managing pain and preventing admissions. Community pharmacists will be asked about: extra time and costs required to: deliver the service, provide any extra facilities, and / or attend any service-related training. For example, there may be costs associated with longer opening hours, or with disposal of more out-of-date stock.

For sample group 3, health care professionals will be asked about in-practice gaps and challenges in service provision. Participants will be asked about cost/resource implications for their own services as well as the perceived effectiveness of the enhanced service at facilitating patient and carer medicines access, managing pain and prevention of hospital admissions comparative to community pharmacy services without enhanced services.

Interview guides will be piloted prior to use.

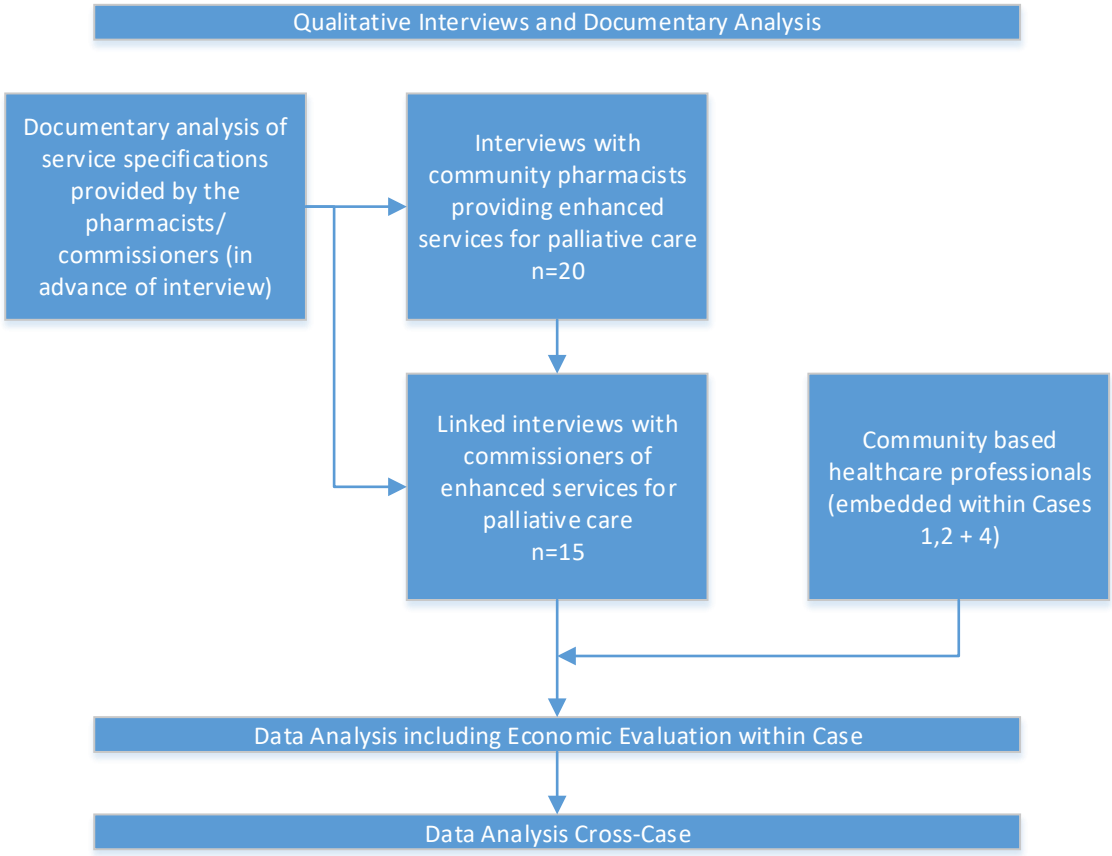
Interviews will continue until data saturation is achieved.

Service-related documents as data sources and documentary analysis

Commissioner and pharmacist interviewees will be asked to provide copies of all documents specific to current service provision, including (where available): specified community pharmacy selection criteria; service level agreements/specifications, including costs of provision or tariffs and formulary medicines stocked as part of the service (as well as stock quantities); audit requirements of the service; and information sheets for healthcare professionals.

These will act as data sources and will undergo documentary analysis (47) as part of the analysis for this case. The focus will be on: financial incentives (or otherwise) for providing the service; community pharmacy service locations and numbers in relation to local/regional population demographics and need; the range of medicines on the stocked list (whether there is a focus on just in case/anticipatory medicines alone) and any enhanced opening hours. This will provide a framework analysis of key features of commissioned services across a range of typical models.

Diagrammatic Representation of Case 3



Economic evaluation:

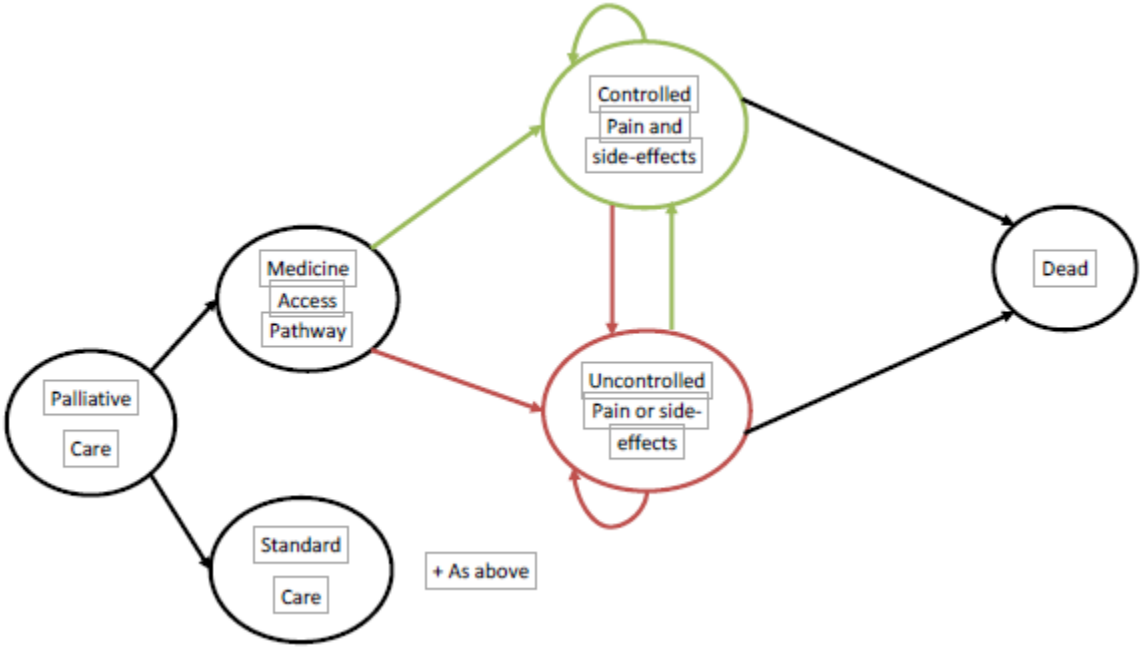
We will conduct an economic evaluation comparing the case study care pathways vs. standard care following the NICE reference case. Standard Care will be defined following consultation with the project team and Study Advisory Group and will either be one of the Phase 3 case study service delivery models or another pre-defined model describing the most common configuration of services in practice. The analysis will be from the perspective of the healthcare and personal social service provider and the main outcome cost per incremental quality-adjusted life year (QALY). We will use the patient record data to capture typical resource use for each service, including resources that are part of the planned pathway and unplanned service use (e.g. unplanned GP visits and hospital stays). These will be costed using standard unit cost resources including the PSSRU report and NHS Reference costs. A supplementary analysis will adopt a wider cost perspective, including patient and carer costs (for example, relating to travel) based on information from previous research (i.e. IMPACCT).

We will use a decision-analytic model, developed in previously funded NIHR research programmes (4, 16) to estimate cost-effectiveness. The existing Markov model will be adapted for the current setting and to accommodate the data available. The likely structure of the decision model is outlined in Figure 1. We believe that the most likely benefit to patients of optimal medicines access is good and timely control of symptoms - principally pain and of opioid-related side-effects. Research suggests that these factors have the greatest impact on patient QoL. For this reason, pain and side-effect control will be the mechanism for capturing intervention benefits in the decision model. While access to medicines will likely have benefits for the control of other symptoms such as breathlessness and agitation, we feel that the additional complexity and data requirements in capturing all of these is not warranted in the current context.

The model will have a daily or weekly cycle and patients will transit between the controlled and uncontrolled pain/side-effect health states according to the effectiveness of the particular medicines access strategy. Those with controlled pain and well-managed side-effects will have better HRQoL

and lower costs. Further details on the modelling, for example, how long it is reasonable to assume that a patient remains in the uncontrolled pain state, will be determined in consultation with patients and clinicians in the team as part of the model adaptation process.
Model parameter values are already available for the costs and HRQoL of the controlled and uncontrolled pain health states, for pain progression over time and for survival for those receiving palliative care. We may adjust the cost parameters with additional data from this study. The two pieces of data we lack are the costs and effectiveness of the individual medicines access pathways. The costs will be generated in the case note review and supplemented with any relevant data from the systematic review (Phase 1) and healthcare practitioner survey (Phase 2). The case note review will likely not provide complete data on either pain levels or whether pain or side-effects are controlled. However, it will inform on whether individuals have received emergency/unplanned healthcare due to uncontrolled pain. This will be used as a proxy in the model and represent our measure of effectiveness for the economic evaluation. This data will allow the calculation of the probability that patients remain in control of their pain and opioid side-effects for each of the medicine access strategies. This will be supplemented with information from the systematic review (Phase 1).
We will also gather effectiveness data in the survey (Phase 2) – for example, on typical time to medicines access for patients and this measure of timeliness will be incorporated in the model. We will explore with the team and in piloting the optimal question format to elicit this information. We will also use data from the patient logs to inform the effectiveness values if suitable. The time horizon of the model will be six months by which time close to 100% of the cohort would have died.

Figure 1: Proposed Decision-Analytic Model Structure



The modelling will allow us to generate expected costs, benefits and incremental cost-effectiveness ratios (ICERs) based on QALYs in the standard way for each of the services vs. standard care. Clearly, those medicine access strategies that enable faster or more consistent control of pain and side-effects will provide higher QALY gains and lead to lower healthcare resource use by reducing unplanned visits and admissions. We will use the NICE preferred willingness to pay threshold range of £20,000-£30,000 per QALY gained and consider ICERs below this to denote a cost-effective intervention. We will use extensive deterministic sensitivity and scenario analyses to assess the impact of model parameter changes on cost-effectiveness. We will conduct probabilistic sensitivity analyses (42) to assess overall uncertainty in the model and represent this in cost-effectiveness planes, cost-effectiveness acceptability curves (43) and frontiers and net monetary benefit distributions.

For Case 3, qualitative interview data and documentary analysis assessing costs and resources associated with this service model, as well as estimates of effectiveness, will be collated. This will be combined with other data (e.g. from the survey) to estimate the cost effectiveness of the enhanced service model using an existing decision-analytic model. In order to estimate the effectiveness of the service, interviewees will be asked about their perceptions of the effectiveness of the service in relation to pain control and prevention of hospital admissions comparative to community pharmacy services without enhanced service provision (as above). Service level agreements will be used as data sources to outline the payments made to community pharmacies to provide such services, as well as lists of the medicines stocked under the enhanced services, and the numbers of pharmacies providing the service. There will be extensive mapping of service provision to outline the full economic costs of such service provision.

Case study data analysis:
Data from each embedded sub-unit within each case will be triangulated (data source and method triangulation) to build an in-depth, contextual understanding of medicines access experience in each delivery model.

Cross case comparison
On completion of data analysis for each case, we will use cross-case comparison for theory-building (37). This will include some comparison of descriptive statistical data as part of describing and evaluating medicines access features across cases. Importantly, recommendations from the comparative evaluation of service delivery cases will be developed through the construction of a framework of indicators characterising good practice in medicines access. This framework will be built from the Phase 1 systematic review, our PPI consultation and relevant national standards such as NICE (2015) guidance on Care of the Dying Adult (44) and the Faculty of Pain Medicine's CQC Core Standards for Pain Management (45). We anticipate this framework will include indicators such as: speed of access to medicines; patient and carer burden (time, travel, cost, psychological distress) experienced in accessing medicines; number and type of contacts required before a medicine is supplied; accessibility, ease of use and comprehensiveness of information sources; and use of out-of-hours, unplanned or emergency services. The framework will be applied to help evaluate each case and to enable systematic comparisons across cases / service delivery types, thus underpinning recommendations that meet study objectives.

Reliability, validity and rigour:
During data collection and analysis we will employ strategies and techniques to: enhance the reliability and validity of quantitative data (e.g. using agreed Standard Operating procedures, protocols and proformas for standardising data collection and sampling of patients for internal generalisability (above)); strengthen the rigour of qualitative data (e.g. providing a clear audit trail of decisions, using more than one researcher to analyse qualitative data from interviews to enhance the trustworthiness of the coding process, and providing a rich, thick description of the case and findings in the analysis and write up of each case study) to maximise the potential transferability of the findings.

Phase 4: (Objective 7): The objective of Phase 4 is to evaluate supply chain processes and identify challenges in providing access to end-of-life medicines. To this end we will interview community pharmacists exploring the issues identified in the earlier study phases, such as: whether/how feedback from community pharmacists leads to changes in wholesaler/distributor behaviour, as well as the impact of recent policy initiatives on access.

We will conduct a survey using telephone interviews with 20 community pharmacists and approximately 10 key pharmaceutical wholesalers and distributors to evaluate supply chain processes and identify challenges in providing access to EoL medicines. Our recent research (3, 4, 16, 19), initial scope of literature and PPI during proposal development has identified particular problems focused on the supply chain e.g. local pharmacies' insufficient stock of key medicines, and changes to the brands and packaging of medicines. We will use Phase 4 to track back, along the supply chain, and explore issues identified in Phases 1, 2 and 3 on a wider scale with pharmacists and wholesalers / distributors.

Sampling:
Pharmacists: We will use the sample of community pharmacists identified for Phase 3, case 3 (above) for Phase 4 interviews, combing these where possible. We do not anticipate that sampling enhanced pharmacy service providers will influence the nature of views / data on supply chain processes, but if this appears to be the case, we will seek additional interviewees (who do not provide enhanced services) through the CRNs and specialist interest groups such as the Association of Supportive and Palliative Care Pharmacy.

Pharmaceutical wholesalers /distributors: we will use snowball sampling to identify a national sample of interviewees through pharmacists interviewed in Phase 4. Interviewees will include national and short line distributors. Sample sizes are based on achieving likely data saturation.

Data collection:
Semi-structured telephone interviews will be used to interview both pharmacists and wholesalers / distributors. This method will be time-efficient and will enable us to cover a wide geographical area with minimal researcher travel costs (pharmacists) and access wholesalers / distributors who may be more geographically dispersed. Final interview guides will be informed by our Phase 1 systematic literature review, and emerging findings from Phases 2 and 3, but we will collect data on such issues as: wholesaler influences on pharmacy stock levels; wholesaler / distributor decision-making about stock and supplies; whether / how feedback from community pharmacists and / or patients leads to changes in wholesaler / distributor behaviour, as well as impact of recent policy initiatives such as the community pharmacy integration agenda.
Data Analysis:
Data from interviews will be audio-recorded, fully transcribed and analysed using Framework Analysis (9). Interviews with a) pharmacists and b) wholesalers / distributors will be analysed separately and then triangulated to look for differences and similarities in perspectives on supply chain issues that influence patient access to EoL medicines.

Phase 5: (Objectives 8, 9): We will hold a consensus-building workshop, with invited EoL care national experts, to: review study findings; generate recommendations pertaining to EoL service delivery model characteristics that result in responsive, person-centred, coordinated medicines access, and identify and / or construct models to evaluate in a follow on study. Data for this for each of the pathways will be derived from the case note reviews and supplemented with data from targeted literature searches. The modelling would allow us to generate incremental cost-effectiveness ratios based on QALYs, explore different service model cost and outcome scenarios and capture uncertainty using deterministic and probabilistic sensitivity analyses.
Sampling:
Purposive and snowball sampling will be used to identify national experts, including EoL policy, service delivery, professional, and education leads at the Department of Health, NHS England, Health Education England, Royal College of Nursing, Royal College of General Practitioners, Royal Pharmaceutical Society, Health Education England workforce development leads, Clinical Commissioning Group leads for EoL, EoL and Non-Medical Prescribing programme leads from HEIs, charity representatives e.g. Marie Curie, Macmillan Cancer Care, pharmaceutical wholesaler representatives, and key EoL health care professionals. Our PPI co-applicant and Advisory Group PPI members will represent EoL informal carer perspectives.
Data collection and analysis:
We will undertake a preliminary analysis of data from Phases 1-4 to present key findings to workshop participants for debate and discussion. Applicants (SL, AB) used a similar approach in previous research, involving round table discussion and prioritisation of policy and service delivery recommendations (35). Participants' discussion and outputs will be captured in writing for later analysis, focusing on key recommendations and priorities.

Dissemination and projected outputs
The research will provide a robust evidence base to underpin recommendations on service delivery and workforce development to underpin quality EoL medicines access services. Together with Phase 5 key stakeholders, we will build our recommendations on our comparative evaluation of medicines access experiences, costs and outcomes of care within different service delivery models. Study outputs are designed to identify gaps in service provision and deficits in care experienced by patients and carers, as well as highlight models of good practice and the context that supports and embeds these into EoL service delivery. The research will identify critical points for service intervention and workforce development to improve patient access to medicines at EoL. In turn, we expect this will stimulate and inform changes to healthcare policy, clinical commissioning, service organisation, practice delivery, and education and training of nurse and pharmacist prescribers, ultimately leading

to faster and less burdensome routes to medicines access for patients.
Our overall approach to promoting knowledge mobilisation to ensure impact on the management of health services and improvements to practice and service delivery in the NHS focuses on:
• dissemination as an active, continuous process throughout the lifetime of the study, as well as after Final Report submission
• using multiple media to disseminate tailored outputs to a variety of stakeholders in EoL medicines access
• embedding key stakeholders in the Study Scientific Committee (SSC), creating continuous opportunities for knowledge mobilisation at a strategic level
We will use electronic and social media to disseminate information about the study, its progress and findings widely through research, policy, practice, education and service user channels for maximum engagement and impact. We will set up a dedicated, University-supported study website and twitter account to disseminate links to our study, its progress and outputs, outlining policy, practice and workforce implications. We will disseminate the study website link, tailored policy briefs (written with Public Policy @ Southampton) and executive summary through NHS England, the National EoL Care Intelligence Network at Public Health England, National Council for Palliative Care, Marie Curie, Macmillan Cancer Care, Hospice UK, National Institute for Clinical Excellence, Health Education England, Royal College of Nursing Lead for EoL care, Royal College of General Practitioners' Clinical lead for EoL care, Royal Pharmaceutical Society, Palliative Care Pharmacists' Network, Local Pharmaceutical Committees and the Association for Prescribers, as well as dissemination to all Clinical Commissioning Groups in England, maximising use of organisations' portals where possible. We will reach pharmaceutical wholesalers, distributors and retailers through briefing reports targeted to key individuals responsible for supply chain, as well as seeking opportunities to publish in their internal publications. Throughout the study we will use our SSC PPI, policy and practice representatives from key stakeholder organisations (e.g. National Council for Palliative Care, Hospice UK, Local Pharmaceutical Committees, Royal College of Nursing, Royal College of General Practitioners, Health Education England) to act as dissemination and impact champions for the study and its outputs. We will also actively engage in horizon-scanning for opportunities to deploy study outputs to influence relevant EoL care consultations, reviews and policies, and input to relevant EoL service delivery and clinical guidelines.
We will reach practitioners through publicising the study, its progress and findings in professional journals, news outlets and networks e.g. Pulse, Pharmaceutical Journal, Nursing Times, e Hospice and Local Pharmaceutical Committees. We will also present at key practitioner conferences e.g. Royal College of General Practitioners' Annual Conference, Palliative Care Pharmacists Network Annual Conference, Association for Palliative Medicine Supportive and Palliative Care Conference. In addition, we will publish in multidisciplinary, international peer-reviewed research journals and present at research conferences nationally and internationally.
Our PPI co-applicant and SSC reps will act as impact champions and play an active role in identifying local and national contacts for dissemination of study findings to consumer groups and forums. We will meet with our PPI reps to plan outputs targeted at the general public, especially people with life-limiting illness and their family carers. Outputs could include advice leaflets and/or coverage of findings on radio and in national newspapers and/or widely read magazines.
Dissemination and outputs will include:
• A study launch event and press release
• Study website outlining the study and key findings as the study progresses, as well as final implications for policy, practice, workforce, education and research
• Dedicated study twitter account to tweet study launch, headlines and links to outputs
• Briefing events about the study, its progress, opportunities for involvement and outputs, for local NHS stakeholders and practitioners (e.g. GPs, Clinical Nurse Specialist and Community Nurse teams, Local Pharmaceutical Committee members, Medicines Management reps)
• 3 -4 publications in international peer reviewed research journals (e.g. BMJ Supportive and

• Palliative Care, BMC Health Services Research) (prescriber surveys, case studies and community pharmacist / distributor interviews papers)
• Policy briefs targeted at policy makers responsible for EoL care and prescribing services
• 1-2 end of study publications in professional journals (e.g. Pharmaceutical Journal; Pulse; Nurse Prescriber)
• Presentation at conferences: e.g. Palliative Care Congress, Palliative Care Pharmacists
• Network Annual Conference, Health Services Research UK Symposium.
• Executive summary with clearly identified policy, commissioning, workforce, education and
• practice implications.
• Full report detailing all work undertaken, with supporting technical appendices

An important study output will be the development of a proposal for further research to systematically compare the impact of features of service delivery models on patient and carer outcomes through a follow on study of effectiveness and cost effectiveness. Funding will be sought through NIHR.

Project management
The project will be overseen by Professor Sue Latter (SL). A Core Study Team (CST) will be formed, consisting of SL, AR, SRF-S, MB and RF-L. The CST will monitor the day-to-day progress of the project, coordinate tasks and deal with problems. Co-applicants outside the CST will be invited to attend the CST meetings at strategic points based on their expertise and the stage of the project. Dr David Meads will supervise the health economist Research Fellow in Year 2 and 3, reporting monthly to the CST.
A Study Steering Committee (SSC) will be formed, including the CST and all other co-applicants, and will meet four times face-to-face during the study. The SSC will monitor overall progress, coordinate phases of research, discuss problems and oversee the budget and financial issues and review findings. The SSC will oversee the strategic progress of the project by reviewing the success of each key stage of the project against the monitoring framework, which will include the research timetable. The SSC will advise the CST at key decision-points.

Ethical considerations
The main ethical issues of this study relate to informed consent, anonymity, and information provided to patients and carers – patients (and their carers) receiving palliative care are potentially emotionally, physically and psychologically vulnerable. In Phase 3, we will use a capacity to consent checklist and only recruit patients who have sufficient mental capacity to understand the research process, and who are deemed to have capacity to undertake the requisite elements of data collection for the study. We will re-confirm capacity and consent at key data collection points throughout. All patients, carers and health care professionals (HCPs) invited to take part will be free to decline and this will be made clear before and during their participation. All patients, their carers and HCPs will be given an information sheet detailing the study procedures to allow them to make an informed decision about their participation. In addition, a verbal explanation of the study will be offered ahead of the beginning of each interview, and consent will be checked again at the end. All participants involved in any stage of the study will be reminded of their right to withdraw at any point without giving an explanation.
To ensure anonymity, all participants will be given a unique ID number which will be noted on questionnaires, logs, and interview transcripts, thus preventing participants from being identified. In addition, any identifiable details, such as names of people, places or institutions will be removed from logs, interview transcripts and patient records. Digital recordings will be held on a dedicated secure University server and will only be accessible to those directly involved in the interviews and analysis. All quotations in reports, publication and presentations will be presented in an anonymous format. The contact details of participants will be held securely on a dedicated University server for

the duration of the study, and after this time will be deleted. We plan to submit the relevant documents for ethical approval in months 1-2 (Phase 2), months 4-7 (Phase 3) and months 9-11 (Phase 4) of the study.

Patient and Public Involvement

Active PPI involvement will ensure patient and carer concerns continue to drive study questions and their experiences will inform decisions about the sensitivity and feasibility of study methods. Study recruitment and retention in the EoL context is sensitive: PPI views on the best methods of handling this will be sought. Active involvement of Co-app and SSC PPI members will also ensure that: the patient and carer voice is represented in dissemination of study findings, dissemination materials are designed appropriately for patients and the public, and appropriate dissemination channels are used to maximise public engagement as part of an overall impact strategy.

A bereaved carer (LR) has been recruited to the study team as co-applicant. LR has experience of helping a close relative to access and manage medicines at EoL, as well as experience in collaborating with academics to promote PPI in research and academia, including with NIHR and on a NICE Guideline Development Group for myeloma. LR will join CST meetings at strategic points to input expertise and provide feedback on relevant project materials, and will also attend SSC meetings. At the Southampton site, a patient and a carer group at a local hospice has agreed to be consulted at key stages; at Leeds we will recruit up to 3 patients and carers from a local hospice and The Yorkshire Cancer Patients' Forum to form a PPI panel. We will consult on e.g. preparing ethics submission participant information, and designing dissemination materials Two PPI representatives, recruited via Macmillan Cancer Support, will be members of the SSC. PPI will include both cancer and other life-limiting conditions perspectives. Professor Alison Blenkinsopp is the study lead support for PPI and will e.g. offer to meet PPI members pre-and post-SSC for support and to facilitate input. LR & SSC PPI members will present findings in Phase 5 workshop and help to disseminate findings. They will act as impact champions for the study, working with the team to develop & implement a strategy to maximise public engagement.

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Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Appendix 2 – Overview and rationale for the protocol changes relative to Phase 3 Case 3

Overview

We propose three changes to our original protocol:

1. The research team propose a change to the methods of data collection for one of the case studies in Phase 3 (Case 3). However, the case study design (37) remains as stated in version 1 of the study protocol (v1 12.12.17) for all cases.

2. Related to 1., we propose, where possible, to combine Phase 4 community pharmacist interviews with interviews that we will conduct with community pharmacists in our revised Phase 3 Case 3 design.
3. To identify service delivery models for end of life care, we have analysed the literature from our systematic review (Phase 1), our Phase 2 survey data and discussed our findings with our SSC members. As a result, we believe that our four case studies represent the range of both typicality and innovation in current service delivery models of end of life care. We believe that the study resource for Phase 3 is therefore best spent evaluating these four cases (with a re-modelled, extended case site 3, equivalent in scale to two sites) rather than attempt to identify another two insufficiently distinct service delivery models to make up six case sites as originally planned.

Rationale for the focus on community pharmacy enhanced services for palliative care

Although commissioned to provide better patient access to palliative care medicines, the ActMed study Phase 2 national survey data suggests that the functioning of these services may be sub-optimal. Over half of the survey sample were not aware of community pharmacies in their area that provide an enhanced service for palliative care (690/1329; 52%). A small proportion of respondents (122/1329; 9.2%) stated there was no provision in their area, but importantly only 39% of the sample were aware of such services in their area (517/1329). There were also clear differences between healthcare professional groups in awareness levels: 220 palliative care clinical nurse specialists (57%) were aware of these services in their area, 69 primary care pharmacists (45%), 92 community pharmacists (42%) and 39 community nurses (39%); with the lowest levels of awareness held by General Practitioners (111 or 22% of the GP sample).

Of the overall 39% (517/1329) of health care professionals who were aware of these services, 84% (433) believed that they facilitated speed of access to medicines for patients/carers. However, there were differences in opinions by healthcare professional group (highest levels of agreement were for General Practitioners at 92%, then primary care pharmacists 91%, and community pharmacists 85%; dropping to 79% for community based palliative care clinical nurse specialists and community nurses 74%, who represent the two professional groups most likely to utilise enhanced services on behalf of patients/carers).

Our research to date has also revealed that community pharmacy services, while covering one third of the country, are under-researched and little is known about them. Therefore the research team propose that these services are an important area for further investigation via in-depth mixed method case study. However, the methods of data collection need altering to suit the case.

In order to best evaluate the impact of community pharmacy delivered enhanced services for palliative care (on demand availability of specialist drugs) we propose a remodelled case study design. Here we present our rationale for the revised case study design, describe the extensive scoping work we have undertaken to inform the proposed case study, and the links that we will create with our other case studies and with Phase 4.

To inform the case study design we have:

- Analysed geographical spread of provision and commissioning models nationally
- Interrogated our Phase 2 survey responses and identified potential participants, with further snowball sampling planned
- Held discussions with service commissioning teams in two areas
- Remained mindful of NIHR carbon footprint guidance while recognising it might be necessary to include sites beyond our original Yorkshire/Hampshire focus

Rationale for changes to data collection methods

Extensive feasibility work has been carried out regarding suitable sites for an enhanced service pharmacy case study including in-depth interrogation of responses from community pharmacist Phase 2 survey respondents as a possible sampling frame, feasibility discussions with Medicines Optimisation Teams from two CCGs within reach of the research team (including informal interviews with these teams) and further discussion about feasibility with enhanced service community pharmacists in practice.

This feasibility work has provided important contextual background to current enhanced service provision, including highlighting best methods for data collection as well as issues that warrant further systematic investigation in this case study. A key issue in relation to a potential case study focused on enhanced community pharmacy services for palliative care concerns our **inability** to link patients using specific pharmacies providing an enhanced service back to a small (2-3) number of GP practices for sample recruitment.

We have concluded that there is no reliable way of identifying patients who use a particular local enhanced service from GP practices. We have checked out with a number of GPs that the Electronic Prescribing Service (EPS) (whereby patients nominate a preferred pharmacy) operates insufficiently precisely in practice to allow us to link patients to a named enhanced service community pharmacy. Furthermore, prescribing of Controlled Drugs via the EPS has only just being introduced, thus further confounding any reliable link between EPS and identified pharmacy use.

Alternatively, difficulties likely to impede patient and pharmacist recruitment through community pharmacies are: lack of awareness by community pharmacists as to which of their patients are palliative; high levels of corporate chain pharmacy provision, with resulting uncertainty about corporate governance agreement to study participation; high pressures on community pharmacists' time due to workload; and general lack of familiarity with, and history of community pharmacy involvement in, research.

Our scoping work to date indicates that we are likely to experience challenges in recruiting community pharmacists for data collection, and we wish to capitalise on the willingness to participate in our study expressed by our Phase 2 community pharmacist respondents. In addition, we believe a sensible use of the research team resource would be to use to combine community pharmacist interviews for Phase 3 and 4.

Timescale

We plan to run data collection for Phase 3 Case 3 concurrently with data collection in our other case sites.

Timescale for data collection with pharmacists and commissioners:

April: re-establish contact with Phase 2 survey respondents; pilot interview guide; set up interviews

April – June: interviews with community pharmacists and request documents on service provision; snowball sampling for further community pharmacist interviews; identification of commissioner sample through snowball and purposive sampling

July-September: transcription of pharmacist interviews; pilot commissioner interview guide; set up commissioner interviews, request documents on service provision and interviews with commissioners

October-December: transcription of commissioner interviews; analysis of pharmacist, commissioner and health care professional interview data (including health economic analysis); documentary analysis

Data from health care professionals (sample group 3) will be captured as part of interviews in case sites 1, 2 and 4, and will not therefore require extra resource or time (it is expected that some interviews may be extended by a maximum of 5-10 minutes).

We anticipate that overall, the revised case study will provide a robust analysis of community pharmacy palliative care enhanced service provision and its impact on patient and care access to medicines. Drawing on the perspectives of a purposive sample of key stakeholders, and using triangulation of data will enable us to build an in-depth understanding of the current strengths, challenges and areas for development of this model of service delivery, resulting in recommendations for policy on commissioning and practice to facilitate patient and carer access to medicines at end of life.

Appendix 3: Study Flowchart