The Prognosis in Palliative care Study II (PiPS2): PROTOCOL

Long title of the trial	The Prognosis in Palliative care Study II (PiPS2): A multicentre prospective, observational, validation cohort study.
Short title of trial	The Prognosis in Palliative care Study II (PiPS2)
Version and date of protocol	Version 2.0, 29-Jan-2017
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Phase of trial	Phase III prognostic validation study
Sites	Multi-site
Chief investigator:	Professor Patrick Stone p.stone@ucl.ac.uk
Sponsor Representative:	Rajinder Sidhu r.sidhu@nhs.net

SIGNATURES

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

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

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

Chief Investigator: Professor Patrick Stone

Sign: 

Date: 19th April 2016

Sponsor Representative: Rajinder Sidhu

Sign:

Date: 19th April 2016

VERSION HISTORY

Version number	Version date	Reason for Change
1	29-Feb-2016	Original protocol
1.1	19-Apr-2016	a) Name and contact details of study manager inserted b) Copyright acknowledgment for Confusion Assessment Method and PPSv2 c) Instructions for scoring PPSv2 d) Information sheets and consent/declaration forms removed from protocol appendices and upload separately to REC e) Letters to GP removed
2.0	29-Jan-2017	a) To continue recruitment until we have obtained 1,267 complete data sets rather than relying on multiple imputation to account for missing data, or restricting recruitment to only those patients who are able to provide a blood test. The total sample size has therefore increased to 1,778 b) Appendices 6 and 7 added. These describe a qualitative sub-study to assess the acceptability (to patients, their carers and clinicians) of using prognostic models

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2 LIST OF ABBREVIATIONS

Term	Definition
AMTS	Abbreviated Mental Test Score
APR	Annual progress Report
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CPS	Clinician Prediction of Survival
CRP	C-Reactive Protein
CTU	Clinical Trials Unit
DSH	Data Safe Haven
ECOG	Eastern Co-operative Oncology Group
FNP	Feliu Prognostic Nomogram
GCP	Good Clinical Practice
GSF	Gold Standards Framework
HRA	Health Research Authority
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
IG	Information Governance
KPS	Karnofsky Performance status
LACDP	Leadership Alliance for the Care of Dying People
LCP	Liverpool Care Pathway
MCA	Mental Capacity Assessment
MOREcare	Methods of Researching End of Life Care
NHS	National Health Service
PaP	Palliative Prognostic score
PiPS	Prognosis in Palliative care Score
PiPS-A	Prognosis in Palliative care Score - A
PiPS-B	Prognosis in Palliative care Score - B
PIS	Patient information sheet
PPI	The Palliative Prognostic Index

PPS	The Palliative Performance Scale
REC	Research Ethics Committee
ROC AUC	Receiver Operating Characteristic Area Under the Curve
SAE	Serious Adverse Event
Term	**Definition**
SMG	Study Management Group
TTD	Time to Terminal Disease
UCL	University College London

3 TRIAL PERSONNEL

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4 SUMMARY

Title: The Prognosis in Palliative care Study II (PiPS2): A multicentre prospective, observational, validation cohort study.

Short title: The Prognosis in Palliative care Study II (PiPS2)

Objectives: Primary aim: To compare PIPS-B against clinician predictions of survival (CPS) and to validate PiPS-A&B.

Secondary aims:
To validate PaP, FPN, PPI and PPS.
To determine the acceptability of prognostic models/methods to patients, carers and clinicians and to identify potential barriers to clinical use.

Study design: This is a multi-site, prospective, cohort, validation study of a prognostic indicator in palliative care patients with advanced incurable cancer, with a qualitative sub-study in selected participants.

Methods: A range of prognostic scores will be calculated (PiPS, PaP, PPI, PPS, FPN) and compared with CPS.

Data collection will include; assessments by clinicians (demographic details, ECOG performance status, PPS, KPS, Observer-rated global health status, AMTS, pulse rate, CPS and TTD); blood results (white blood count, lymphocyte count, neutrophil count, platelet count, albumin, alkaline phosphatase, alanine transaminase, c-reactive protein, lactate dehydrogenase and urea); clinical signs and symptoms (presence or absence of key symptoms; anorexia, delirium, dysphagia, dyspnoea, fatigue, peripheral oedema, decreased oral intake, weight loss); and measures of disease extent (nature and site of primary and sites of metastases).
Patients will be flagged with HSCIC and the accuracy of the prognostic estimates will be compared against actual survival.

The qualitative sub-study will consist of interviews with

	patients, relatives and healthcare professionals.
Study duration per participant:	Participants will undergo a single baseline visit and their records will be flagged with HSCIC so that the study team are informed when the patient dies. Participants in the qualitative sub-study will undergo a single interview.
Estimated total study duration:	36 months
Planned study sites:	This is a multi-site study of hospice inpatient palliative care units, community palliative care teams and hospital support teams from across England and Wales.
Total number of participants planned:	1,778 patients
Main inclusion/exclusion criteria:	<u>Inclusion criteria</u> Participants with advanced incurable cancer, with or without capacity to consent to research, aged 18 years or over, who have been recently referred to palliative care services will be eligible. The qualitative sub-study will include a purposive sample of patients, carers and clinicians <u>Exclusion criteria</u> Currently receiving (or planned to receive) potentially curative treatment for cancer.
Statistical methodology and analysis:	<u>Descriptive analysis</u> Predictors and the outcomes will be summarised using descriptive analysis. Categorical predictors will be reported as raw numbers and percentages. Continuous variables will be summarised using mean or median and standard deviation or interquartile (IQ) range as appropriate. The percentage of values missing for each predictor will also be presented. The survival times of patients will be summarised using median and IQ ranges and Kaplan Meier

graphs.

Validation of PiPS models

The discriminatory ability of the models will be assessed using the C-statistic. Separate C-statistics will be calculated for the "two weeks" and the "two months" models. We will also assess model performance by plotting Kaplan-Meier survival curves for each of the three risk groups identified by the PiPs models ("days," "weeks," and "months+"). Model calibration will be assessed by comparing observed and predicted probabilities.

Comparison between PiPS model and clinician predictions

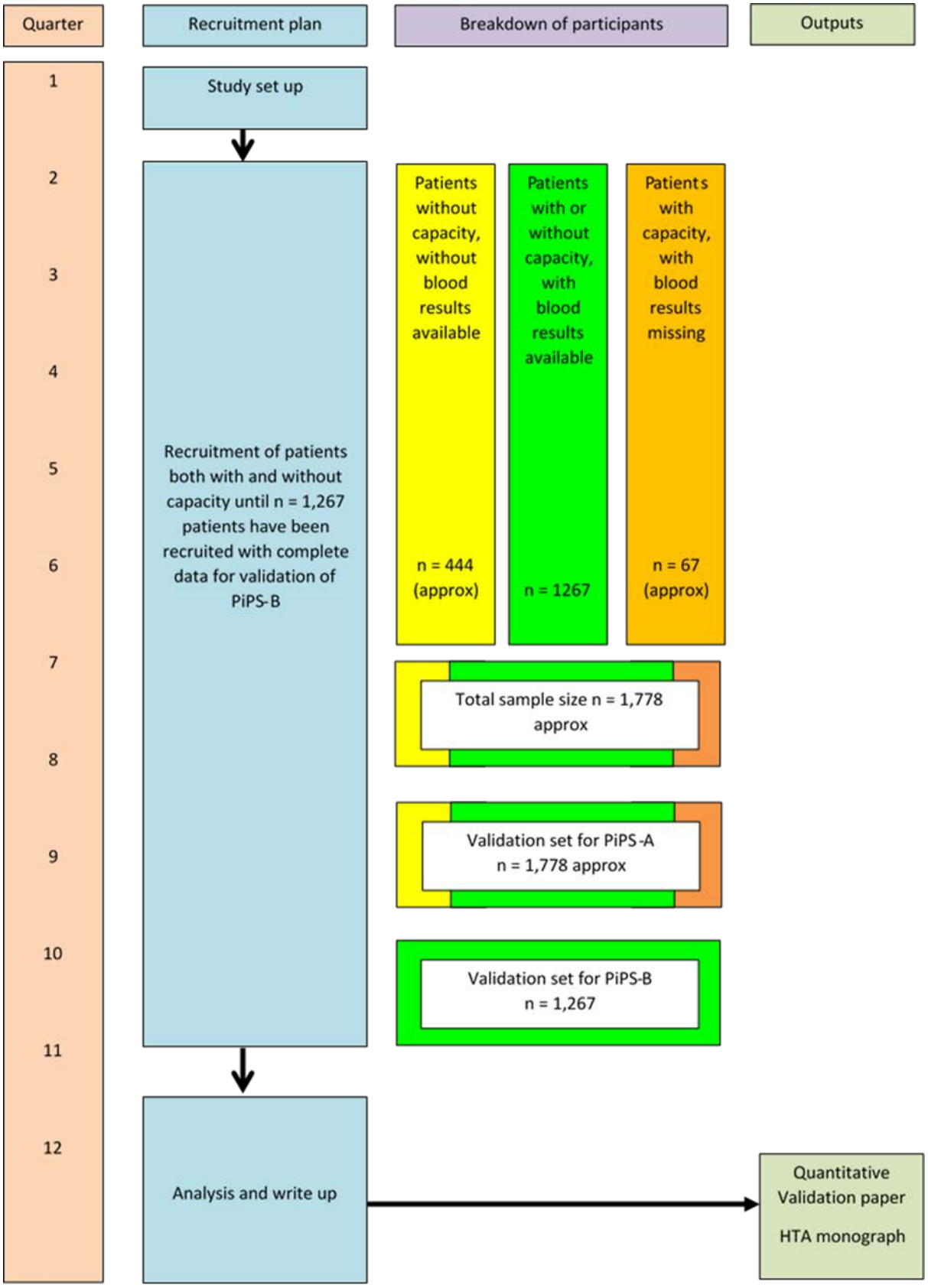
To compare the accuracy of the model and clinicians' predictions, the primary analysis will focus on the PiPS-B model. McNemar's test will be used to compare the proportion of overall patient deaths predicted correctly by PIPS-B with the corresponding proportion predicted correctly by clinicians.

Qualitative sub-study

Interview data will be entered into NVivo 10 and analysed using the five stages of Framework Analysis.

5 TRIAL FLOW CHART

Flow chart - The Prognosis in Palliative care Study II (PiPS2)



6 INTRODUCTION

6.1 BACKGROUND

Systematic identification of patients approaching the “end-of-life” is a key recommendation of the Department of Health end-of-life care strategy [1]. The Gold Standards Framework (GSF) service improvement programme (widely used in general practice, nursing homes and increasingly in acute hospitals) uses a needs-based coding system dependent upon whether patients are expected to live for “days”, “weeks”, “months” or “years” [2]. However, many patients who would potentially benefit from inclusion in such programs are currently unidentified by clinicians. Improved prognostication would benefit patients and their carers by providing them with better quality information to inform their choices about future care. Improved prognostication would also help clinicians to plan services and to ensure that patients are cared for in the most appropriate environment and with the most appropriate treatments. If the prognostic scores being studied in this research can be shown to be accurate and reliable then non-specialist clinicians will be able to use this method to identify patients entering the last few days, weeks or months of life. This will facilitate access to specialist services, inclusion of patients on "end-of-life" electronic communication systems and will aid the identification of patients approaching the end of life. Prognostic scores could also facilitate comparison of services by more accurately describing the case-mix of referrals.

Studies show that patients, carers and clinicians all value accurate prognostic information [3-7]. The number of elderly patients with advanced cancer is anticipated to increase substantially over the next twenty years. The results of our research are therefore highly likely to remain relevant and important to NHS needs in the future. This proposal will contribute to the development and refinement of existing prognostic tools. Our primary aim is to validate PiPS A&B (see below) in palliative care patients with advanced incurable cancer. A secondary aim is to determine the acceptability of prognostic models/methods to patients, carers and clinicians and to identify potential barriers to clinical use (see Appendix 6 and 7).

6.2 CLINICAL DATA

The PiPS A&B prognostic models were developed (by members of our research team) in a cohort of patients with advanced cancer, no longer undergoing disease-modifying treatment, newly referred to specialist palliative care services, whom were followed up for at least three months or until death [8]. A total of 1018 participants (across 18 sites) were recruited prospectively to the original study. Logistic regression identified 11 core variables (pulse rate, general health status, mental test score, performance status, presence of anorexia, presence of any site of metastatic disease, presence of liver metastases, serum C-reactive protein, white blood cell and platelet count and serum urea) that were independently predictive of both two-week and two-month survival. Four variables had

prognostic significance for two week survival only (dyspnoea, dysphagia, bone metastases and alanine transaminase) and eight variables had prognostic significance for two month survival only (primary breast and male genital cancer, tiredness, loss of weight, lymphocyte and neutrophil count, alkaline phosphatase, and albumin). Separate prognostic models were created for patients without or with available blood results (PiPS-A and PiPS-B respectively). The Receiver Operating Characteristic Area Under the Curve (ROC AUC) for all models varied between 0.79 and 0.86. The PiPS A&B models were able to categorise patients into three prognostic groups; those with a survival of "days", "weeks" or "months+". The differences between the variables included in PiPS-A and PiPS-B are summarised in Table 1.

Table 1 – Variables included in PiPS-A and PiPS-B

Variable	PiPS-A	PiPS-B
ECOG performance status	X	X
General health status	X	X
Abbreviated Mental Test Score >3	X	X
Primary breast cancer	X	
Primary prostate cancer	X	X
Distant metastases (any)	X	X
Liver metastases	X	
Bone metastases	X	X
Anorexia	X	X
Dysphagia	X	
Dyspnoea at rest	X	
Weight loss in last month	X	
Pulse rate	X	X
Fatigue		X
Albumin		X
Alkaline phosphatase		X
Alanine transaminase		X
C-Reactive protein		X
Lymphocyte count		X
Neutrophil count		X
Platelet count		X
Urea		X
White blood count		X

Two recent studies have been published [9, 10]. Baba and colleagues [9] undertook an independent validation of the PiPS models in approximately 2000 Japanese cancer patients. The authors reported that the PiPS instrument performed as well as in Gwilliam's original study [8]. Interestingly the study included several hundred patients who were still undergoing palliative chemotherapy (whereas the population in the original study was patients who had stopped all treatment). Sensitivity analysis indicated that PiPS worked as well in patients on palliative chemotherapy as in other patients. Unfortunately the Japanese

paper has a number of limitations. Most importantly the study did not compare the accuracy of PiPS to the accuracy of clinicians' survival estimates, or to the accuracy of other prognostic tools. Moreover the study did not include any qualitative work to assess the acceptability or feasibility of using PiPS in clinical practice. Finally, due to the different epidemiology of cancer in Japan and differences in health care systems the study did not address the validity of the PiPS prognostic instruments in a UK cancer population. The second study [10] was much smaller (n = 202) and the study population was palliative cancer patients in a specialist cancer hospital in South Korea. The authors reported that the PiPS instruments performed approximately as well as in the original paper (although overall accuracy was less). The study population had a shorter survival than that studied in the PiPS development study with fewer patients surviving for "months". Taken together, these two new papers do not diminish the need for the study we propose. Indeed, they lend greater weight to the importance of undertaking a large scale validation study in the UK using clinician predictions (and other prognostic tools) as comparators.

Based on the results of systematic reviews [11, 12], we have identified four other prognostic models suitable for further evaluation. The Palliative Prognostic Index (PPI) [13] and the Palliative Performance Scale (PPS) [14], like PiPS-A, can both be calculated without the need for blood results. The PPI is calculated using five clinical variables (from the Palliative Performance Scale [PPS], oral intake, the presence or absence of dyspnoea, oedema and delirium). The model stratifies into three groups; survival shorter than three weeks, shorter than six weeks, or more than six weeks. The PPS is a measure of functional status and is one of the variables included in the PPI score. Although not specifically designed as a prognostic instrument the PPS has been found to have prognostic significance in patients with advanced disease [15, 16]. However, because the PPS was not specifically designed as a prognostic instrument, key indicators (e.g. symptom scores) were not included in the development stage and the PPS therefore lacks some face validity as a stand-alone prognostic tool.

The Palliative Prognostic (PaP) score [17, 18] and the Feliu Prognostic Nomogram (FPN) [19], like PiPS-B, both require a blood test. The PaP score classifies patients into one of three risk groups. The PaP score is generated by applying a "weighted" score to each of six variables (clinician prediction of survival, Karnofsky performance status [20], anorexia, dyspnoea, total white blood count and lymphocyte percentage). A limitation of PaP is that it is essentially a clinician prediction of survival with a small adjustment for some other prognostic variables: the clinician estimate alone accounts for 50% of the range of scores and clinicians are required to estimate survival with an unrealistic accuracy of +/- two weeks. Consequently PaP scores are of limited use when clinicians are unsure about, or disagree on, likely survival times. The FPN uses five variables (ECOG performance status [21], serum albumin, Lactate Dehydrogenase, lymphocyte counts and time from initial diagnosis to diagnosis of terminal disease [TTD] to predict survival at 15, 30 and 60 days. In the validation study the FPN was found to be more accurate than the PaP [19]. The FPN also

has the advantage over the PaP of not relying on subjective clinician predictions of survival. However, the concept of TTD is itself a rather subjective parameter since it is a matter of judgement as to when cancer becomes "terminal".

6.3 RATIONALE AND RISKS/BENEFITS

In 2014 due to substantial criticism of the Liverpool Care Pathway (LCP), an independent committee chaired by Baroness Neuberger [22] was asked to review LCP use. A particular concern expressed by many relatives and professionals was that clinician predictions of survival were inaccurate and that this had the potential to adversely affect patient care. As a result Neuberger identified several priorities to improve care of the dying, including a specific recommendation that, "…the NIHR should fund research on improving where possible the accuracy of prognostic tools". More accurate methods of prognostication are likely to lead to significant improvements in the quality of care of dying patients. A frequent theme of the Neuberger report was that clinicians need more reliable tools to help them to prognosticate and that research needs to be undertaken to determine the best way to present this information to patients, relatives and carers, and to determine the barriers to routine clinical use. The Leadership Alliance for the Care of Dying People [23] (LACDP) was given the responsibility of responding to the Neuberger review and its response has identified the recognition of dying as one of the five key priority areas for improving end-of-life care [24].

This research addresses the problem of identifying the best method to accurately predict survival in patients with advanced incurable cancer. This research will compare the accuracy of PiPS prognostic scores with clinician predictions of survival and with other prognostic models (PaP, FPN, PPI and PPS) in a variety of appropriate clinical settings (hospice, community and hospital).

Although clinician estimates of survival have been shown to be inaccurate and over-optimistic [25] it is vitally important that they are included as a comparator in any evaluation of prognostic scores, since this is the method by which most clinicians currently form their opinion regarding likely survival. Our own work in this area has suggested that a multi-disciplinary estimate of survival is more accurate than a nurse's estimate of survival [26]. Accordingly, the current study will compare the accuracy of PiPS-B against either a doctor's, a nurse's or a multi-professional estimate of survival.

6.4 ASSESSMENT AND MANAGEMENT OF RISK

Our study (although observational rather than interventional) raises several ethical issues.

6.4.1 EMOTIONAL DISTRESS

There is potential for patients and/or relatives/carers to be distressed at the thought of being involved in a research project concerning prognosis. However, experience with our previous study showed that, in general, most patients are happy to be involved in this type of research. We did not receive any complaints from patients or family members that

involvement in the research was distressing. Nonetheless we remain sensitive to this possibility and have sought to engage users/consumers in the design of the study in order to minimise any potential upset. All potential research subjects will already be under the care of a palliative care team and are therefore likely to be well aware of their limited prognosis. However, before being approached about the research project patients will be screened by the palliative care team and when clinical staff deems that involvement in the research project would cause an undue risk of emotional distress then such patients/families will not be approached. Any patients who are upset by mention of prognosis will receive appropriate support from palliative care clinical services, including onward referral to counselling or psychological support services if necessary.

6.4.2 PHYSICAL DISTRESS

Study participants with capacity are required to donate a 15mls sample of venous blood for analysis. There is potentially some minor physical discomfort associated with this. In order to minimise distress every attempt will be made to "piggyback" study blood tests onto routine blood tests already being taken as part of standard clinical care (this is one of the reasons why we do not want patients to undergo an enforced delay before participating in the research study). When recently-obtained blood results are available then these results will be used, rather than obtaining a fresh specimen.

Patients without capacity will not be required to have a blood test, but if blood is being taken for another (clinical) reason then those additional results required for the study will be "piggy-backed" onto the request form.

6.4.3 INCONVENIENCE

For patients with capacity, involvement in this study requires time to read the Patient Information Sheet (PIS) and provide consent. Patients will then need to answer a few brief questions about the severity of their symptoms, undergo a brief physical examination (check pulse rate) and provide a 15mls venous blood sample for analysis. In addition clinicians will need to determine whether patients score greater than 3/10 on the Abbreviated Mental Test Score [27]. This will not usually require clinicians to ask all of the 10 items included in the questionnaire. Total contact time to obtain research data is approximately 10 minutes. We are aware that time is precious to patients with a terminal illness and that is why patient contact has been kept to an absolute minimum, and most study data will be obtained from patients' records or clinicians' observations rather than directly from patients.

For patients without capacity the only patient contact required will be to measure pulse rate (if that has not already been recorded by clinical staff). No questionnaires or blood tests are required. All other study data will be extracted from patient notes or after discussion with the clinical team.

6.4.4 INTRUSION

At the time of giving consent to participate in the study, patients (or the relatives/carers of patients without capacity) will also need to give permission for research staff to access medical records in order to extract study specific data. In order to minimise intrusion and avoid distress, patient records will be flagged with the NHS Health and Social Care Information Centre (HSCIC) so that the research team are informed when the patient has died.

6.4.5 DATA PROTECTION

This study involves the collection, transfer and storage of patient identifiable and sensitive data. Information governance (IG) and data protection are therefore crucially important to the successful running of this research. This study conforms to the UCL IG Framework. The IG Framework consists of UCL policies, procedures and guidance around data protection and information security and is governed by a management framework. It aligns with relevant legislation and regulations and provides suitable evidence to meet requirements of HSCIC IG Toolkit and ISO27001:2013.

Paper based screening logs containing patient identifiable data and pseudonymised case report forms will be maintained and stored securely at each participating site. All information from the screening logs will be remotely entered to the UCL Data Safe Haven (DSH) on a weekly basis. The pseudonymised data on the case report forms will be remotely entered to the study database (provided by Sealed Envelope). Both systems comply with all relevant data protection legislation

7 OBJECTIVES

The overall aim of this research is “the validation of models of survival to improve prognostication in advanced cancer care to include the Prognosis in Palliative care Study (PiPS) predictor models”. Because PiPS-B performed better than PiPS-A in the development study [8], and to avoid multiple testing, only PiPS-B will be directly compared against the accuracy of clinicians’ predictions.

7.1 PRIMARY

To validate PiPS-A&B and to compare PIPS-B against clinicians’ predictions of survival

7.2 SECONDARY

To validate PaP, FPN, PPI and PPS

8 OUTCOMES

A range of outcome measures to assess prognostic accuracy will be studied. We have selected measures that are suitable for use in patients with or without capacity and for those in whom a blood test would or would not be appropriate.

8.1 PRIMARY OUTCOMES

The primary outcomes of interest will be the survival of the participants (measured from date of study entry) and the predictions of the PiPS-A and the PiPS-B prognostic models. Both models provide a prediction about whether a patient is likely to live for "days" (less than 14-days), "weeks" (2 to 7 weeks), or "months +" (2 months or more).

8.2 SECONDARY OUTCOMES

The secondary outcomes will be the predictions produced by the PPI (less than 3week survival, 3 to 6 week survival, and greater than 6 week survival); PPS (probability of dying within 7, 14 or 28 days); FPN (risk of dying within 15, 30 or 60 days); PaP (risk of dying within 30 days).

8.3 SAMPLE SIZE AND RECRUITMENT

8.3.1 SAMPLE SIZE CALCULATION

To compare clinician and PiPS-B predictions

PiPS-B is the primary model of interest for this research. Table 2 (below) shows the overall percentage agreement between clinicians and the PiPS-B risk model, and the actual observed proportion of deaths from the original developmental cohort study published by Gwilliam et al [8] based on 553 patients for whom these pairwise data were available. The overall proportion of patients with discordant predictions from clinicians and the model was 41%. In 23% of patients the clinicians were incorrect and the risk model correct when compared to observed survival whereas in 18% of patients the clinicians were correct and the model incorrect. To show at least a 5% improvement in correct predictions (in terms of overall agreement with observed patient survival giving an odds ratio of 1.28) when using the model compared to clinicians' predictions, assuming 80% power and 5% significance level and using a McNemar's test, a total of 1,267 patients will be required. The formula and software used for this calculation are based on Machin 2009 [28].

Table 2 – Concordant and discordant predictions in the original developmental cohort

	Clinician predictions compared to observed deaths	
Risk model predictions compared to observed deaths	% of patients where predictions were correct	% of patients where predictions were incorrect
% of patients where predictions were correct	24	23
% of patients where	18	36

predictions were incorrect		

Percentages have been rounded up to the nearest integers.

Validation of PiPS-B and PiPS-A models

To validate predictions from a risk model it has been recommended that the validation data must be large enough to precisely fit a model with one predictor and thus it has been recommended that the validation data should have at least 100 events. The validation data for the proposed study will involve several centres. There is no guidance on sample size calculation for multi-centre validation data and whether there is any impact on sample size of clustering of patients within centres. We expect clustering of patients within centres to be minimal based on other studies in community care. However, to be conservative we have inflated the number of events required in the validation data to 150. To calculate the sample size for the validation exercise we have used the lowest observed event rate from the original developmental cohort study [8] (percentage of patients who died within days) to obtain a conservative estimate. Assuming an event rate of 26.9%, based on the cohort study we will need a minimum of 560 patients (rounded up) to validate the PiPS-A model. In fact, we will recruit 1,778 patients in total, most of who will be able to provide data for validation of PiPS-A.

Assuming an event rate of 17.8% based on the cohort study by Gwilliam *et al* [8] we will require 843 patients to validate the PiPS B model. However, we will in fact recruit 1,267 patients (see above sample size for PiPs B) which will allow us to validate models with an event rate of 11.8% or higher. The other risk models included in the validation exercise are PaP (which predicts probability of survival at 30 days), FPN (which predicts probability of survival at 15, 30 and 60 days), PPI (which predicts probability of survival at 21 and 42 days) and PPS (which can be used to predict probability of survival at 7, 14, 28 days). We do not expect the prevalence of any of these prognostic groups to be lower than 11.8%. Thus the sample size of 1,267 should be adequate to validate all these models.

Total sample size

Different sample sizes are required to validate PiPS-A (n = 560) and PiPS-B (n = 1,267) [see above]. PiPS-A scores can be calculated in any patient (regardless of capacity and regardless of whether or not they can provide a blood test). We will require at least 560 patients to validate the PiPS-A and based on our previous experience developing this model we estimate that the validation population will consist of approximately 466 patients with and 94 patients without blood results. The majority of patients with blood results will be patients with capacity (although a few patients without capacity may also be included if they are having a blood test taken for another clinical reason). All of the patients without blood results will lack capacity.

We will continue to recruit patients to the study until we have obtained 1,267 participants with blood results (the validation set for PiPS-B), at which point recruitment will stop. Based

on our previous experience we estimate that the final sample size will be 1,778 participants (consisting of 511 patients without blood results and 1,267 with blood results). However, the final sample size may be slightly smaller or larger than this depending upon the proportion of included patients with blood results actually recruited.

8.3.2 PLANNED RECRUITMENT RATE

Centres will be initiated on a rolling programme over the first six months of the study. We have therefore anticipated an incremental increase in recruitment rates as the study progresses, reaching peak recruitment 6 months after study initiation.

Study month	Date	Recruitment per month	Cumulative total
3	July 2016	20	20
4	August 2016	25	45
5	September 2016	35	80
6	October 2016	100	180
7	November 2016	100	280
8	December 2016	100	380
9	January 2017	100	480
10	February 2017	100	580
12	March 2017	100	680
13	April 2017	100	780
14	May 2017	100	880
15	June 2017	100	980
16	July 2017	100	1080
17	August 2017	100	1180
18	September 2017	100	1280
19	October 2017	100	1380
20	November 2017	100	1480
21	December 2017	100	1580
22	January 2018	100	1680
23	February 2018	100	1780

9 STUDY DESIGN

9.1 OVERALL DESIGN

A multi-centre, prospective, observational, cohort study of patients with advanced, incurable cancer who have recently been referred to palliative care services in order to validate various prognostic models.

The study is designed to show whether the PiPS prognostic models are more accurate at predicting survival that a clinician's estimate. The study will also provide information to validate other prognostic tools; PPS, PPI, PaP and FPN.

Patients will be recruited shortly after referral to the palliative care service and will be "flagged" with HSCIC so that the project team are notified when the patient has died.

9.2 RECRUITMENT

9.2.1 PATIENT IDENTIFICATION

Patients will be recruited in three settings; community palliative care teams (including day hospice and outpatients), hospital palliative care teams and inpatient palliative care units. In each participating service a screening log will be maintained, by members of the clinical team, of all new referrals to the service. For patients who are not eligible to participate the screening log will record the following information; age, gender, reason for ineligibility.

9.2.2 PATIENT APPROACH

All eligible patients (or their relatives if the patient lacks capacity) should be approached by a member of the clinical team about participation in the study. If eligible patients are not approached by a team member then the reason for failure to do so should be recorded in the screening log. Common reasons for clinical staff not approaching an eligible patient are likely to include; patient/family previously expressed a wish not to be approached about the study; patient died before possible to approach; patient discharged from the service before possible to approach; or clinical team judge that discussion of the research project would cause psychological harm to patient or family.

9.2.3 PATIENT RECRUITMENT

Potential participants (or the relatives of patients without capacity) who are approached by a member of the clinical team will be asked if they would be willing to speak to a member of the research team and will be handed a patient/carer information leaflet. A member of the research team will then discuss the study with the patient/relative and will seek consent/agreement to participate. For community patients this discussion about the study may occur by telephone. If the patient/relatives decline to participate in the study then the reason for this (if known) should be documented on the screening log.

10 SELECTION OF PARTICPANTS

Any patient recently referred to the participating palliative care service should be considered for inclusion in the study provided they meet the inclusion and exclusion criteria.

10.1 INCLUSION CRITERIA

a) Patients who have been recently referred (or re-referred) to palliative care service. For inpatient palliative care patients (including hospital support teams), "recent" referral means that the patient should have been first seen by a member of the palliative care team no more than 7-days previously. For a community, day-hospice or palliative care

outpatient, “recent” means that the patient should have had fewer than three previous contacts with the palliative care service before they are recruited to the study.

b) Patients with locally advanced or metastatic, incurable cancer.
c) Aged 18 years or over.
d) Sufficient English language skills for patients with capacity to understand study literature and undertake study assessments. Whenever possible translation services will be used to maximise the potential for patients or carers to give consent/agreement to participate.

10.2 EXCLUSION CRITERION

a) Currently receiving (or planned to receive) treatment with curative intent. Patients receiving palliative treatment will still be eligible to participate.

11 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

11.1 PARTICIPANT IDENTIFICATION

All participating patients will be known to palliative care services. Only those patients or relatives judged by the clinical team to be eligible will be approached by the study team. The decision about whether or not to approach patients will be recorded in a screening log. The screening log will be kept at each site to track the number of eligible patients, the number approached and the number consented.

11.2 INFORMED CONSENT PROCEDURE

11.2.1 ASSESSMENT OF CAPACITY

The clinical team will make an assessment about whether patients have capacity to participate in the study or whether a consultee (personal or nominated) will be required to advise about research participation. Capacity will be assessed by the attending clinician using Department of Health guidance [29]. If capacity is in doubt the clinician will carry out a four point capacity test (see below) and will document the answers on the Royal College of General Practitioners’ MCA Toolkit for Adults in England and Wales (2011).

- Can the person communicate their decision?
- Can they understand the information given to them?
- Can they retain the information given to them?
- Can they balance, weigh up or use the information?

11.2.2 PATIENTS WITH CAPACITY

For patients with capacity a member of the clinical team will provide a Patient Information Sheet (PIS) and, if patients are agreeable, a researcher will fully explain the aims, methods, anticipated benefits or risks of the study and will explain to the participants that they are

under no obligation to enter the study and that they can withdraw at any time during the study, without having to give a reason. For community patients this discussion with a researcher may occur over the telephone.

Written informed consent will usually be obtained at least 24 hours after the PIS has been handed out. However, since this observational study is not very burdensome to participants, our experience from previous research has shown that many individuals would prefer to proceed with the study straight away. This may be because (for instance) it would be inconvenient to delay participation, or because the patient is due to be discharged home that day and does not wish to miss the opportunity to participate in the study. All patients will be advised that it is usual practice to wait at least 24 hours before committing to participate in the research. However, those patients who would prefer to proceed immediately will be permitted to do so.

A copy of the signed informed consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes. All research staff will be suitably qualified and experienced and will be trained In Good Clinical Practice (GCP). They will have been delegated this duty by the PI on the delegation log. All research staff will receive training in how to discuss study involvement sensitively with this potentially vulnerable patient group. If study involvement raises any issues or concerns with patients or relatives about their own prognosis, then those concerns will be passed onto the clinical team.

11.2.3 PATIENTS WITHOUT CAPACITY

It is important that we include patients who lack capacity because many patients at the end of their lives become confused, semi-conscious, comatose or may have pre-existing cognitive impairment. The study population must be representative of those patients commonly seen in terminal care. We have used guidance from the Mental Capacity Act (2005) and experience from previous research to guide our approach to involving patients without capacity in PiPS2. We do not wish to exclude a significant proportion of patients that this study is intended to help. Therefore for patients without capacity we will utilise a personal consultee to provide assent, which will be the designated next of kin. For patients with no next of kin we will seek the advice of a nominated consultee. The nominated consultee will probably be another doctor working in the hospital/hospice. In the hospital setting the nominated consultee is likely to be a doctor working outside the palliative care team. In the hospice setting where there may not be a doctor outside the palliative care team the nominated consultee will either be another senior doctor in the hospice (who is not involved in the research), a hospice social worker, a chaplain or the patient's GP.

For patients without capacity the first approach to the personal/nominated consultee will come from a member of the clinical team, this may either be in person or on the telephone. The clinical team member will explain the general purpose of the study, provide them with an information leaflet, and will ask the consultee if they are happy to be approached by the

research team. If the consultee is agreeable then a member of research team will make contact with the personal consultee either in person or on the telephone and will discuss the details of the study and will seek the opinion of the consultee about involvement of the patient in PiPS2. In a similar manner to the approach adopted for patients with capacity, consultees of patients without capacity will be advised that it is usual practice to wait for 24 hours before giving assent. However, since this observational study is not very burdensome to participants, if consultees advise that the patient may be enrolled in the study straight away then this will be permitted.

If the consultee gives telephone advice for the patient to be included in the study but he/she is unable to visit the unit to provide written evidence of agreement (i.e. a signed "agreement" form) then verbal agreement will initially be deemed sufficient to allow the research team to enrol the patient in the study and obtain relevant data from the notes. However, in these circumstances an "assent" form will be posted to the relative/carer to be signed and returned to the research team within two weeks of the patient being enrolled in the study. If no signed “assent” form is received then the patient will be withdrawn from the study and all data destroyed.

11.2.4 PATIENTS WITH FLUCTUATING CAPACITY

Patients who temporarily lack and then recover capacity will be informed about their involvement in the study and will have the opportunity to withdraw or confirm participation. This recruitment process was the approach taken in the PiPS developmental study [8].

11.3 SCREENING PERIOD

Once a study centre becomes “active” a screening log will be maintained of all new referrals to the service. The screening log will record the total number of referrals to the service during the recruitment period, the number of eligible patients, the number of patients who are approached by the research team and the number of patients who consent to participate in the study.

11.4 BASELINE ASSESSMENTS

There are four categories of data to be collected about study participants.

11.4.1 INFORMATION OBTAINED FROM MEDICAL/NURSING NOTES OR DISCUSSION WITH CLINICAL STAFF

- Documentation of capacity to consent to participate in the study
- Demographic details of participating patients
  - Age
  - Gender
  - Current location (e.g. home, hospital, hospice)

  - NHS number, name, address and date of birth are temporarily required for “flagging” with HSCIC. Once date of death has been entered into study database and audited, patient data can be anonymised
- Nature and site of primary cancer
- Sites of metastases
- Eastern Co-operative Oncology Group (ECOG) Performance status [21]
- Palliative Performance Scale (PPS) [14]; this modification of the Karnofsky performance score is calculated using observer ratings of ambulatory status, activity, disease extent, self-care abilities, oral intake and conscious level.
- Karnofsky performance score [20].
- Observer-rated global health status; How would you rate this patient’s overall health during the past week? From 1 = very poor to 7 = excellent
- Abbreviated Mental Test Score (AMTS) [27] – if patients are unable to co-operate in obtaining an AMTS score (coma, delirium etc…) they will be allocated a score of 0/10
- Pulse rate measured over one minute.
- Clinician estimates of survival.
  - The attending doctor and nurse will estimate survival independently. When the estimates agree then this will represent the combined multi-professional prediction. When they are discordant, the doctor and nurse will discuss the case and reach a consensus. This method was used successfully in the original PiPS development study [26]. For comparison with PiPS, clinicians will estimate date of death in one of the same three categories used by the model; “days” (less than 14 days), “weeks” (between 14 and 55 days) and “months+” (56 days or more). In order to characterise the prognosticators in more detail they will be asked to provide information about themselves (i.e. age, gender, professional training and years of specialist experience).
- Time to terminal disease (defined as time elapsed between diagnosis and development of incurable disease) - clinicians will be asked to estimate the date on which the disease became terminal. This will usually be the date at which metastatic or recurrent disease was discovered. Sometimes the disease will have been considered terminal from the point of diagnosis.

11.4.2 BLOOD RESULTS

Either obtained as a fresh specimen (patients with capacity) or from blood results obtained as part of routine clinical care within 72 hours of study entry (patients without capacity). No blood specimens will be taken from patients without capacity solely for the purpose of the study.

- Haematology; white blood count, lymphocyte count, neutrophil count and platelet count.

- Serum biochemistry; Albumin, Alkaline phosphatase, Alanine transaminase, C-reactive Protein, Lactate Dehydrogenase and Urea.

11.4.3 CLINICAL SIGNS AND SYMPTOMS

This information will be obtained from the patient directly, from discussion with relatives/carers if the patient is unable to provide it, or from a review of the hospital of hospice notes.

- Presence or absence of key symptoms; anorexia, delirium, dysphagia, dyspnoea, fatigue, peripheral oedema, decreased oral intake, weight loss.

11.5 SUBSEQUENT ASSESSMENTS

At least three months after all recruitment has ended a list of study participants (name, date of birth, address and NHS number) will be sent to HSCIC in order to determine dates of death.

11.6 LABORATORY PROCEDURES

Blood specimens will be processed locally in the routine clinical laboratory using usual arrangements.

11.7 DEFINITION OF END OF TRIAL

The study will end after the required sample size for validation of PiPS-B has been recruited (n = 1,267) or three years after study initiation whichever is the earliest.

11.8 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND 'STOPPING RULES'

Participants will be free to withdraw from the study at any stage without giving a reason.

11.9 POST-TRIAL ARRANGEMENTS

Due to the nature of the disease process it is unlikely that any participants will still be alive at the end of the study. However, those patients who remain alive and wish to make use of the validated prognostic tools will be free to do so.

12 DATA MANAGEMENT AND QUALITY ASSURANCE

12.1 CONFIDENTIALITY

All data will be handled in accordance with the UK Data Protection Act 1998.

12.2 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Data will be collected from patients themselves (if able to answer questions), from clinical staff and from inspection of the medical notes and electronic patient records.

Data will initially be collected on a paper screening log. The screening log will contain anonymised information about all referrals to the clinical service for the duration of the study and will identify the reasons why patients were not eligible for the study, if they were approached about the study (and reasons why not approached) and whether they consented to the study. The log will also contain identifiable data from patients who consented to participate. Anonymised data from non-participants and identifiable data from study participants will be uploaded to the Data Safe Haven (DSH) at UCL Data from the screening log using a secure web-link. Data will be uploaded on approximately a weekly basis.

Patients who consent to the study will be allocated a unique study identifying number from the site screening log. Study data will be entered onto a paper-based case report form and de-identified data and will then be securely transferred to an electronic web-based database (*Sealed Envelope*).

12.2.1 SCREENING LOG

The screening log will be paper-based and will include the following information on all new referrals to the participating service: age, gender, whether patient eligible for study (if not, why not), whether patient has/has not capacity, whether patient/consultee has been approached by a member of the clinical team about the study (if not, why not), whether patient/consultee agreed to speak to a member of the research team (if not, why not), whether patient/consultee agreed to participate in the study (no reason for non-participation need be given, but if a reason is volunteered this will be recorded). For patients who are enrolled in the study the screening log will also record: name, date of birth, address, NHS and unit number.

The data on the screening log will be uploaded periodically (approximately once/week) to the Data Safe Haven at UCL.

12.2.2 CASE REPORT FORM

The case report form will be paper-based and will include the following information:

Pseudo-anonymised participant identifiers

- Study number
- Study site
- Current location (Home, Hospital inpatient, Hospital outpatient, Hospice inpatient, Hospice outpatient/day care, Care home)
- Participant initials
- Age
- Gender
- Date of study enrolment

Medical diagnosis

- Primary tumour
- Sites of metastases

Clinical condition

Presence or absence of key symptoms or clinical findings

- Anorexia, dysphagia, dyspnoea at rest, fatigue, weight loss in last month, oral intake
- General health status
- Presence of clinically apparent ascites
- Presence of clinically apparent peripheral oedema
- Presence of delirium – Appendix 1
- Pulse
- Abbreviated Mental Test Score - Appendix 2
- Eastern Co-operative Oncology Group (ECOG) performance status – Appendix 3
- Karnofsky performance scale - Appendix 4
- Palliative Performance scale - Appendix 5
- Time to Terminal Disease – time between diagnosis and development of incurable disease.

Blood Results

For patients with capacity a fresh blood specimen must be taken. For patients without capacity there is no requirement to take a fresh blood specimen, however if a blood sample taken is being taken for another reason as part of routine clinical care within 72 hours of study enrolment then the relevant tests should be included on the request form. Similarly if blood results are available from a previous test taken within 72 hours of study enrolment then these results should be recorded.

The blood results required are; Albumin, Alkaline phosphatase, Alanine transaminase, C-reactive protein, Lactate dehydrogenase, lymphocyte count, neutrophil count, platelet count, urea, white blood count.

Doctor prediction of survival

- Information about the doctor making the prognostic estimate – Speciality, grade, years of experience, years since qualification, years working in palliative care, length of relationship with patient, time since last assessment
- Estimate of length of survival
- Estimated probability of survival to specific time points - 1 day; 3 days; 7 days; 15 days; 30 days and 60 days

Nurse prediction of survival

- Information about the nurse making the prognostic estimate – Speciality, grade, years of experience, years since qualification, years working in palliative care, length of relationship with patient, time since last assessment
- Estimate of length of survival
- Estimated probability of survival to specific time points - 1 day; 3 days; 7 days; 15 days; 30 days and 60 days

MDT estimate of survival

If doctor and nurse independently agree on approximate length of survival then that is the agreed MDT estimate. If they disagree then they should confer and agree an MDT response.

Date of death

Dates of death will be obtained from HSCIC three months after completion of study.

12.3 DATA HANDLING AND ANALYSIS

Data will initially be in the form of paper-based records stored securely at the study sites. There will be two paper records; a screening log (for all referrals) and case-report forms for all study participants. The screening log will provide a unique study identifier for each participant. This study number will be used on the case report form together with the patient's initials and date of birth.

12.3.1 SCREENING LOG DATA

Approximately once per week the data in the study screening log will be entered into the Data Safe Haven (DSH) at UCL. The SLMS Data Safe Haven technical infrastructure has been built specifically to host sensitive data. The hosting is on a thin client system with dual factor authentication. This is a multi-user system with permission-based access control. There is a standard process for granting and revoking access and system privileges are limited to a small number of technical staff who have received training in information security. The system is only used for hosting sensitive data.

12.3.2 CASE REPORT FORM DATA

The case report forms will be pseudonymised using a unique study number obtained from the local screening log. When data collection is complete (other than date of death), the case report form will be entered onto a web-based online database (hosted by *Sealed Envelope*). "*Sealed Envelope*" is an independent data management company commissioned by the Priment Clinical Trials Unit to support data management for the PiPS2 study. All data is instantly mirrored to another server located elsewhere in the UK so that even in the event of a natural disaster it will be possible to recover services quickly. All databases are also backed up daily to tape and kept for two weeks. *Sealed Envelope* is registered with the Information Commissioner's Office (ICO) and is inspected by the MHRA, the UK clinical trials regulator.

12.4 DATA OWNERSHIP

At the end of the trial, the data belongs to UCL.

13 RECORD KEEPING AND ARCHIVING

All essential documents will be archived for a minimum of 20 years after completion of trial. Destruction of essential documents will require authorisation from the Sponsor.

14 STATISTICAL CONSIDERATIONS

Rumana Omar is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

14.1 STATISTICAL ANALYSES

14.1.1 Summary of baseline data and flow of participants

Descriptive analysis

Initially the predictors and the outcome will be summarised using descriptive analysis. Categorical predictors shall be reported as raw numbers and percentages. Reports of continuous variables shall include mean or median and standard deviation or interquartile (IQ) range as appropriate. The percentage of values missing for each predictor will also be presented. The survival times of patients will be summarised using median and IQ ranges and Kaplan Meier graphs.

14.1.2 Primary outcome analysis

Validation of PiPS models

We will validate the PiPS models as they were presented for use in the original study by Gwilliam and co-workers [8]. For both PiPS-A and PiPS-B, two separate models have been developed to predict the two week (14 day) and two month (56 day) survival of patients (thus generating three prognostic categories; less than two weeks, two weeks to two months and greater than two months). The week and month models include different sets of predictors. For both models (weeks and months), if the predicted probability of the event exceeded 50% for a patient, then the patient was classified to have the event. Otherwise it was assumed that the patient did not have the event. Thus if, for example, the models predicted that a patient would survive two weeks, but predicted that the patient would die within two months, then the PiPS model outcome would be that the patient was predicted to die in “weeks”.

The discriminatory ability of the models will be assessed using the C-statistic. Separate C-statistics will be calculated for the “two weeks” and the “month” models. The C-statistic will be estimated by forming all patient pairs and calculating the proportion of patient pairs

where the patient who has the event has the higher predicted value. The PiPS online calculator provides (see www.pips.sgul.ac.uk) a prediction as to whether a patient will survive for days, weeks or months. The model calibration will be assessed by comparing the observed and the predicted proportions for each of these categories. The calibration of the prognostic models will be further assessed using the calibration intercept and slope based on a logistic regression model fitted to the validation data using the predicted log-odds as the only predictor [30]. This will also be done separately for the "two weeks" and the "month" models. The calibration intercept and slope, and the C-statistic will initially be estimated without taking account of potential patient clustering within centres. In a second analysis, these performance measures will be calculated for each centre separately (assuming most centres have sufficient number of events to allow such calculations) and the estimates pooled across centres using a weighted average [31]. The calibration intercept and slope, and the C-statistic will be presented as estimates with confidence intervals.

We will also assess model performance by plotting Kaplan-Meier survival curves for each of the three risk groups identified by the PiPs models ("days," "weeks," and "months+").

Comparison between PiPS model and clinician predictions

To compare the accuracy of the model and clinicians' predictions, the primary analysis will focus on the PiPS-B model. McNemar's test will be used to compare the proportion of overall patient deaths predicted correctly by PIPS-B with the corresponding proportion predicted correctly by clinicians. Table 3 (below) will form the basis of this comparison.

Table 3 – Blank table for analysis comparing PiPS-B predictions with clinicians' predictions

	Clinician predictions compared to observed deaths	
Risk model predictions compared to observed deaths	% of patients where predictions were correct	% of patients where predictions were incorrect
% of patients where predictions were correct		
% of patients where predictions were incorrect		

14.1.3 Secondary outcome analysis

As part of the secondary analyses we will combine the models' predictions for the two week and two month cut-off points to produce a categorical prediction of survival ("days," "weeks," or "months/years") and compare with clinicians' estimates and the corresponding

observed values descriptively with respect to their accuracy . Table 4 (below) will be used for this descriptive comparison (the cells will contain the counts in each category).

Table 4 – Blank table for analysis of secondary outcomes

	Actual Survival		
Clinician Predictions	Days	Weeks	Months
Days			
Weeks			
Months			
	Actual Survival		
Model Predictions	Days	Weeks	Months
Days			
Weeks			
Months			

Linear weighted κ will be also used to compare the performance of the clinicians with that of the models. If appropriate we will also consider using the net reclassification index (NRI) as part of this secondary analysis to compare clinician and model predictions, noting that NRI needs to be used with caution, particularly when there are three or more risk categories [32-35].

As part of the secondary analyses, the other risk models (PaP, FPN, PPI and PPS) will also be validated.The calibration of these prognostic models will be assessed using the calibration slope [30] based on a logistic model for binary outcomes and Cox model for survival outcomes[36]. Graphical comparisons of the observed and predicted risks for clinically relevant patient risk groups will also be made. Clinically relevant time points will be used for comparisons for survival outcomes. Model discrimination will be assessed using the C-statistic for binary outcomes and C-index for survival outcomes [35]. The predictions made by the other prognostic models under evaluation in this project will also be compared with the corresponding observed outcomes and clinician predictions (where available). Potential missing data in predictor values will be handled as described.

14.1.4 Sensitivity and other planned analyses

Characteristics of patients with potential missing data will be compared with those with complete information to investigate any bias. Multiple imputation based on chained equations [37] will be used to impute missing predictor values if considered necessary. In our previous study the outcome was complete and about 5% of the predictor values were missing with the exception of C-Reactive Protein (CRP) for which 13% of data were missing.

15 NAME OF COMMITTEES INVOLVED IN TRIAL

15.1 STUDY MANAGEMENT GROUP

The PiPS2 study management group (SMG) will consist of the five co-applicants, the study manager and two user representatives. The SMG will meet face-to-face three times per year and monthly by teleconference in between face-to-face meetings, to direct the running of the study and prepare reports for the Health Technology Assessment (HTA).

Prof. Stone will have ultimate responsibility to deliver the research to high ethical and academic standards, on time, and within budget. The Study Manager will manage the study and will work with the study administrator and the research team at UCL. Prof. Omar will direct the work of the Statistician. Prof Stone will be responsible for the overall running of the study and will work closely with Joanne Palmer (study operations manager) at PRIMENT to oversee the work of the IT/database manager and QA manager. The PIs in Derby, Manchester and Birmingham will manage the research nurses at each site. The international developers of comparison prognostic scoring systems (PaP, PPI, and FPN) have also agreed to act as (unpaid) advisors on the current project (Marco Maltoni, Tatsuya Morita and Jamie Feliu)

There will not be a Data Safety and Monitoring board as it is not an intervention study.

15.2 STUDY STEERING COMMITTEE

A study steering committee (SSC) will be established consisting of three members (a senior academic palliative care clinician who will be the independent chair, a statistician and a user representative). The SSC will meet annually during the study.

The role of the SSC will be to provide overall supervision for the study on behalf of the study sponsor and study funder and to ensure that the study is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The main features of the SSC will be as follows:

- To provide advice, through its Chair, to the Chief Investigator(s), the Study Sponsor, the Study Funder, the Host Institution and the Contractor on all appropriate aspects of the trial
- To concentrate on progress of the study, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the study participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan

- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the study

16 ANNUAL PROGRESS REPORTS

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. The Chief Investigator will prepare the APR.

17 SAFETY MANAGEMENT

17.1 NOTIFICATION OF ADVERSE EVENTS

In line with guidance from the HRA, any adverse event that occurs which is deemed to be serious, related to the research and unexpected will be reported to the ethics committee within 15 days of the principal investigator becoming aware of the event. Principal investigators are required to report all such events to Priment by email to primentsafetyreport@ucl.ac.uk . The Priment SAE form should be used.

17.2 NOTIFICATION OF URGENT SAFETY MEASURES

If it is necessary for the study sponsor or investigator to implement an urgent safety measure in order to protect research participants against any immediate hazard to their health or safety, this will be notified to the ethics committee within 3 days of the measure being implemented.

17.3 NOTIFICATION OF SERIOUS BREECHES TO GCP AND/OR THE PROTOCOL

The sponsor will notify the ethics committee in writing of any serious breach of:

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

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor's SOP on 'serious breaches' will be followed.

18 MONITORING AND INSPECTION

A monitoring plan will be established for the study based on a risk assessment. The study will be monitored with the agreed plan.

The investigators will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants will be

informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

The PI will assume responsibility for the enrolment of eligible patients and for the conduct of the study in accordance with the protocol and applicable regulations this includes training the site staff on their responsibilities

Study monitoring will be performed in accordance with PRIMENT SOP #29 (Clinical Trial Monitoring v1.2).

19 ETHICS AND REGULATORY REQUIREMENTS

NHS ethical approval and Trust Research and Development approvals will be obtained before the study starts. The Patient Information Leaflet, Consultee information leaflets, Consent form (for patients), Documentation of advice forms (for consultees) and letters to GP are enclosed as Appendices (1-3 and 9-13).

Priment will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory bodies, prior to any participant recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Within 90 days after the end of the study, the CI/Sponsor will ensure that the main REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The CI will supply the Sponsor with a summary report of the study, which will then be submitted to the main REC within 1 year after the end of the study.

19.1 PUBLIC AND PATIENT INVOLVEMENT

As part of the PiPS development study we included a survey of patients' views about obtaining prognostic information [26]. The majority (478/778, 61%) of competent patients who participated in PiPS1 indicated that, if accurate information was available, they would want to know their prognosis, 176 (23%) would prefer not to know and 124 (16%) were ambivalent (did ‘not know’ or ‘not care’ about the issue). This reaffirms the importance of the clinical question but highlights the importance of ensuring that prognostic information is not “thrust upon” patients who would rather not receive it. In preparation for this application we undertook a more in depth consultation with seven individual cancer patients and one focus group of users consisting of a further eight carers/patients. All users agreed that the subject was an important area for clinical research. We asked users to reflect upon the involvement of non-competent patients in the study and in whom we should undertake blood tests. Service users stressed that non-competent patients should be

recruited, but only contribute observational measurements. A voluntary coordinator of the Wales Clinical Trials Unit (CTU) Research Partner Group has reviewed our study proposal previously.

Two service users will be recruited by via Marie Curie *Expert Voices* users group. The representatives will participate in regular Study Management Group meetings to discuss issues arising and ensure smooth running of the study. Representatives will be asked to help disseminate study results via patient groups, conferences and co-authorships. Additionally, one user representative will be recruited to the Study Steering Committee.

20 FINANCE

This study is funded for 3 years by the NIHR HTA Programme

21 INSURANCE

University College London holds insurance against claims from participants for injury caused by their participation in the study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this study is being carried out in an NHS organisation or an organisation contracted to the NHS, an NHS organisation or an organisation contracted to the NHS continues to have a duty of care to the participant of the study. University College London does not accept liability for any breach in the NHS organisation or an organisation contracted to the NHS's duty of care, or any negligence on the part of NHS organisation employees. This applies whether the NHS organisation is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this study without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Organisations selected to participate in this study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

22 PUBLICATION POLICY

Study results will be published in peer-reviewed, indexed, journals using an open access format, and the results will be presented at academic conferences. Authorship eligibility will

be in accordance with The International Committee of Medical Journal Editors. All proposed publications will be accord with UCL publication policy.

23 STATEMENT OF COMPLIANCE

The study will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

24 APPENDICES

24.1 APPENDIX 1 – SHORT CONFUSION ASSESSMENT METHOD

I. ACUTE ONSET AND FLUCTUATING COURSE

a) Is there evidence of an acute change in mental status from the patient's baseline? No ____ Yes ____

b) Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity? No ____ Yes ____

II. INATTENTION

Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said? No ____ Yes ____

BOX 1

III. DISORGANIZED THINKING

Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject? No ____ Yes ____

IV. ALTERED LEVEL OF CONSCIOUSNESS

Overall, how would you rate the patient's level of consciousness?

-- Alert (normal)

-- Vigilant (hyperalert)
-- Lethargic (drowsy, easily aroused)
-- Stupor (difficult to arouse)
-- Coma (unarousable)

Do any checks appear in the box above? No ____ Yes ____

BOX 2

If Inattention and at least one other item in Box 1 are checked and at least one item in Box 2 is checked a diagnosis of delirium is suggested.

24.2 APPENDIX 2 – ABBREVIATED MENTAL TEST SCORE

AGE must be correct		
DATE OF BIRTH exact		
TIME without looking at clock or watch, and correct to nearest hour		
YEAR Exact, except in January when previous year is OK		
NAME OF PLACE may ask type of place, or area of town		
RECOGNISE TWO PEOPLE point at nurse and other, ask: 'Who is that person? What does she/he do?		
42 WEST STREET give this (or similar) address twice, ask patient to repeat immediately (to check it has registered), and test recall at end of procedure		
START OF FIRST WORLD WAR Exact year		
NAME OF PRESENT MONARCH		
COUNT FROM 20 TO 1 backwards, may prompt With 30/29/28, no other prompts; patient may hesitate and self-correct but no other errors (tests concentration)		
CHECK RECALL of address and enter score above		
	TOTAL SCORE Out of 10	

24.3 APPENDIX 3 - ECOG PERFORMANCE STATUS

Grade *Please circle appropriate grade*	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care, totally confined to bed or chair

24.4 APPENDIX 4 - KARNOFSKY PERFORMANCE STATUS

100%	Normal, no complaints, no signs of disease
90	Capable of normal activity, few symptoms or signs disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes
0	Death

24.5 APPENDIX 5 – PALLIATIVE PERFORMANCE STATUS

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SOCIETY

Palliative Performance Scale (PPSv2)
version 2

PPS Level	Ambulation	Activity & Evidence of Disease	Self-Care	Intake	Conscious Level
100%	Full	Normal activity & work No evidence of disease	Full	Normal	Full
90%	Full	Normal activity & work Some evidence of disease	Full	Normal	Full
80%	Full	Normal activity *with* Effort Some evidence of disease	Full	Normal or reduced	Full
70%	Reduced	Unable Normal Job/Work Significant disease	Full	Normal or reduced	Full
60%	Reduced	Unable hobby/house work Significant disease	Occasional assistance necessary	Normal or reduced	Full or Confusion
50%	Mainly Sit/Lie	Unable to do any work Extensive disease	Considerable assistance required	Normal or reduced	Full or Confusion
40%	Mainly in Bed	Unable to do most activity Extensive disease	Mainly assistance	Normal or reduced	Full or Drowsy +/- Confusion
30%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Normal or reduced	Full or Drowsy +/- Confusion
20%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Minimal to sips	Full or Drowsy +/- Confusion
10%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Mouth care only	Drowsy or Coma +/- Confusion
0%	Death	-	-	-	-

Instructions for Use of PPS (see also definition of terms)

1. PPS scores are determined by reading horizontally at each level to find a 'best fit' for the patient which is then assigned as the PPS% score.

2. Begin at the left column and read downwards until the appropriate ambulation level is reached, then read across to the next column and downwards again until the activity/evidence of disease is located. These steps are repeated until all five columns are covered before assigning the actual PPS for that patient. In this way, 'leftward' columns (columns to the left of any specific column) are 'stronger' determinants and generally take precedence over others.

   Example 1: A patient who spends the majority of the day sitting or lying down due to fatigue from advanced disease and requires considerable assistance to walk even for short distances but who is otherwise fully conscious level with good intake would be scored at PPS 50%.

   Example 2: A patient who has become paralyzed and quadriplegic requiring total care would be PPS 30%. Although this patient may be placed in a wheelchair (and perhaps seem initially to be at 50%), the score is 30% because he or she would be otherwise totally bed bound due to the disease or complication if it were not for caregivers providing total care including lift/transfer. The patient may have normal intake and full conscious level.

   Example 3: However, if the patient in example 2 was paraplegic and bed bound but still able to do some self-care such as feed themselves, then the PPS would be higher at 40 or 50% since he or she is not 'total care.'

3. PPS scores are in 10% increments only. Sometimes, there are several columns easily placed at one level but one or two which seem better at a higher or lower level. One then needs to make a 'best fit' decision. Choosing a 'half-fit' value of PPS 45%, for example, is not correct. The combination of clinical judgment and 'leftward precedence' is used to determine whether 40% or 50% is the more accurate score for that patient.

4. PPS may be used for several purposes. First, it is an excellent communication tool for quickly describing a patient's current functional level. Second, it may have value in criteria for workload assessment or other measurements and comparisons. Finally, it appears to have prognostic value.

Definition of Terms for PPS

As noted below, some of the terms have similar meanings with the differences being more readily apparent as one reads horizontally across each row to find an overall 'best fit' using all five columns.

1. Ambulation
The items '**mainly sit/lie**,' '**mainly in bed**,' and '**totally bed bound'** are clearly similar. The subtle differences are related to items in the self-care column. For example, 'totally bed 'bound' at PPS 30% is due to either profound weakness or paralysis such that the patient not only can't get out of bed but is also unable to do any self-care. The difference between 'sit/lie' and 'bed' is proportionate to the amount of time the patient is able to sit up vs need to lie down.

'**Reduced ambulation'** is located at the PPS 70% and PPS 60% level. By using the adjacent column, the reduction of ambulation is tied to inability to carry out their normal job, work occupation or some hobbies or housework activities. The person is still able to walk and transfer on their own but at PPS 60% needs occasional assistance.

2. Activity & Extent of disease
'**Some**,' '**significant**,' and '**extensive'** disease refer to physical and investigative evidence which shows degrees of progression. For example in breast cancer, a local recurrence would imply 'some' disease, one or two metastases in the lung or bone would imply 'significant' disease, whereas multiple metastases in lung, bone, liver, brain, hypercalcemia or other major complications would be 'extensive' disease. The extent may also refer to progression of disease despite active treatments. Using PPS in AIDS, 'some' may mean the shift from HIV to AIDS, 'significant' implies progression in physical decline, new or difficult symptoms and laboratory findings with low counts. 'Extensive' refers to one or more serious complications with or without continuation of active antiretrovirals, antibiotics, etc.

The above extent of disease is also judged in context with the ability to maintain one's work and hobbies or activities. Decline in activity may mean the person still plays golf but reduces from playing 18 holes to 9 holes, or just a par 3, or to backyard putting. People who enjoy walking will gradually reduce the distance covered, although they may continue trying, sometimes even close to death (eg. trying to walk the halls).

3. Self-Care
'**Occasional assistance'** means that most of the time patients are able to transfer out of bed, walk, wash, toilet and eat by their own means, but that on occasion (perhaps once daily or a few times weekly) they require minor assistance.

'**Considerable assistance'** means that regularly every day the patient needs help, usually by one person, to do some of the activities noted above. For example, the person needs help to get to the bathroom but is then able to brush his or her teeth or wash at least hands and face. Food will often need to be cut into edible sizes but the patient is then able to eat of his or her own accord.

'**Mainly assistance'** is a further extension of 'considerable.' Using the above example, the patient now needs help getting up but also needs assistance washing his face and shaving, but can usually eat with minimal or no help. This may fluctuate according to fatigue during the day.

'**Total care'** means that the patient is completely unable to eat without help, toilet or do any self-care. Depending on the clinical situation, the patient may or may not be able to chew and swallow food once prepared and fed to him or her.

4. Intake
Changes in intake are quite obvious with '**normal intake**' referring to the person's usual eating habits while healthy.
'**Reduced'** means any reduction from that and is highly variable according to the unique individual circumstances.
'**Minimal**' refers to very small amounts, usually pureed or liquid, which are well below nutritional sustenance.

5. Conscious Level
'**Full consciousness**' implies full alertness and orientation with good cognitive abilities in various domains of thinking, memory, etc. '**Confusion**' is used to denote presence of either delirium or dementia and is a reduced level of consciousness. It may be mild, moderate or severe with multiple possible etiologies. '**Drowsiness**' implies either fatigue, drug side effects, delirium or closeness to death and is sometimes included in the term stupor. '**Coma**' in this context is the absence of response to verbal or physical stimuli; some reflexes may or may not remain. The depth of coma may fluctuate throughout a 24 hour period.

24.6 APPENDIX 6 – QUALITATIVE SUB-STUDY PROTOCOL

24.6.1 RESEARCH PLAN AND BACKGROUND

As highlighted in the 2013 Neuberger report [22] a key research priority for the NHS is to determine the best ways to communicate uncertainty to patients and families about prognostic estimates. Previous research has shown that the majority of patients (61%) would want to know their prognosis if such information was available [26]. Our qualitative study arm will explore with patients and carers the type and extent of prognostic information they require and the best (and most sensitive) way to present this to them. It will also identify areas where extra support for patients/carers or extra training for clinical staff is required. This is particularly relevant because in clinical practice it is often the relatives and carers of patients without capacity or semi-conscious patients who most wish to have access to accurate prognostic information.

Research has also shown that clinicians find making prognostic predictions stressful, and as a result tend to avoid doing so [26]. The qualitative study will also ask clinicians about the acceptability and practical utility of using prognostic indicators to support their subjective estimates and any barriers to their use.

24.6.2 STUDY AIM

To determine the acceptability of prognostic models/methods to patients, carers and clinicians and to identify potential barriers to clinical use.

24.6.3 METHODS

A purposive sample of patients, carers and clinicians asked to participate in the quantitative study in the Manchester area (hospice, community and hospital) will also be asked to consider participation in the qualitative study. Semi-structured, face to face interviews will be conducted with approximately 30-40 patients and carers, and approximately 30 clinicians. The final sample size will be determined by data saturation. The setting for the qualitative study will be the Greater Manchester area for pragmatic reasons. The demographic diversity of the Greater Manchester and surrounding areas however will permit us to recruit from a wide range of backgrounds. The patient and carer sample will comprise patients with capacity and carers of patients without capacity, who have agreed to participate in the quantitative study. We will also approach patients and carers who have declined to participate in the quantitative study to explore their reasons for this. We will also ask their views and opinions about the development and use of prognostic tools with palliative care patients and their carers/relatives.

Should recruitment be lower than expected, recruitment would be extended to include patients, carers and clinicians from a wider region.

Initially, all patients and carers in the quantitative study will be invited by clinical staff to be interviewed. As data collection progresses, we will purposively sample patients and carers

according to pre-specified characteristics so that our sample is as varied as possible and represents the views and experiences of a wide range of patients and carers. So, for example, if interim analysis shows we have recruited mostly older women, we will ask recruiting clinicians to only approach patients of a different age and gender about the qualitative study (although recruitment to the quantitative study would still proceed without any such selection bias). Gender and age are known examples of factors that may influence the decision to receive prognostic information [38-42]. Interviews will use topic guides (see Appendix 7) which will be based on reviews of the literature, results of previous consultations with service users and the MORECare recommendations for conducting research at the end of life [43]. Patients and carers will be asked about perceived advantages and disadvantages of receiving prognostic information and how it should be presented to them. The topic guide will be iterative to allow new themes that emerge during interviews to be explored with future participants. Interview duration will be mindful of participants' needs, to ensure that they are not overburdened, but are expected to last less than one hour. Interviews will take place at a venue of the participants' choice.

The clinician sample will be pragmatic and will comprise health care professionals who routinely care for and make prognostic predictions such as Palliative Care Specialists, Oncologists and GPs. Interviews will be interactive and will explore the acceptability of PiPS and other models. Clinicians will be shown the prognostic models, will try them out during interview, and comment on their perceived clinical usefulness (e.g. ease of completion and interpretability of outputs). They will be asked about potential barriers and facilitators to using the models and to discussing prognostic information with patients and carers. Interview duration will not be predetermined but is likely to be around 60 minutes to allow enough time to use the models and for in-depth discussion.

24.6.4 RECRUITMENT OF PARTICIPANTS

Patients or carers for the qualitative study will be initially approached by a member of the clinical team after they have been approached about the quantitative study. At this point patients/carers will be handed the participant information sheet (PIS) for the qualitative study and asked if they would be happy to speak to a member of the research team about the study in more detail. As interviewing patients/carers about prognosis is sensitive and could potentially cause distress, we will employ a researcher experienced in interviewing palliative patients/discussing sensitive topics.

Health care professionals who routinely care for and make prognostic predictions such as Palliative Care Specialists, Oncologists, GPs and specialist nurses will also be approached to take part. All participants will be given at least 24 hours to decide whether they wish to take part and will be told that they are free to withdraw at any time after that. Written consent will be taken prior to the interview.

24.6.5 SCOPE OF THE INTERVIEWS

The interview will be informal and will discuss participants' experiences of being approached or involved with the Prognosis in Palliative Care Study. We will also explore participants' views about the prognostic models/methods and will explore with participants how best sensitive information about survival length should be presented and discussed with patients/carers. We will also explore potential barriers to clinical use.

Patient/Carer interview content will include some of the following topic areas: their experiences of being approached to take part in the PiPS2 prognostic study; attitudes to the development and use of prognostic indicators; views and opinions of how best and the most sensitive way to present prognostic information to patients and or relatives/carers; opinions about the usefulness of such an indicator/tool.

Clinician interview content will include topic areas such as: experiences of making predictions of survival length to patients/carers; what information do clinicians currently share with patients/carers about prognosis and how do they convey it; Opinions on the development and use in clinical practice of prognostic indicators/tools; barriers and facilitators to clinical use.

24.6.6 CONDUCT OF THE INTERVIEWS

Face-to-face interviews will be conducted by the researcher at a location to suit the participant. Generally individuals will be given the opportunity for this to take place in a private side room. However, we envisage that some patients may feel more comfortable for the interview to take place at their bedside, especially if they are feeling particularly unwell. Other participants may wish to be interviewed in the comfort of their own homes.

24.6.7 DATA ANALYSIS

Interview data will be entered into NVivo 10 and analysed using the five stages of Framework Analysis [44]: familiarisation, developing a thematic framework, indexing, charting, and mapping and interpretation. During the first stage (familiarisation) the research team will become immersed in the data [45], by reading and re-reading the transcripts and discussing emerging themes. Next a thematic framework will be developed based on the topic guide [46]. After this, transcripts will be indexed (coded) line by line using the thematic framework, but remaining open to new themes that emerge [47]. Next the data will be entered into a chart so that coded extracts can be attributed to individual participants. Finally participants' views will be compared and contrasted, and the data presented schematically (mapping). Rival explanations will be explored.

24.6.8 EMOTIONAL/PHYSICAL DISTRESS DURING QUALITATIVE INTERVIEWS

Due to the sensitive nature of the research relating to the discussions of prognostic information of palliative care patients, we have developed a distress policy for the researcher completing face-to-face interviews to consider. For the qualitative study we will collect data from patients their relatives/carers and clinical staff shortly (a few days) after

patients have been approached to take part in PiPS2. If the patient/carer becomes upset during the interview, the researcher will ask whether they would like to stop the interview and, if stopped, whether they then wish to resume. If further support is needed, the researcher will link them to existing support mechanisms in the hospice/organisation. All patients will have been referred to palliative care services and any distress detected during the study will be notified to the relevant clinical services for follow up.

24.7 APPENDIX 7 – INTERVIEW TOPIC GUIDE – PATIENTS & CARERS/RELATIVES

24.7.1 AT THE START

We have approached you to ask you to share your experiences of being approached and/or involved with the Prognosis in Palliative Care Study. We would also like to ask your views about the development of a prognosis tool for palliative care patients and what you think about doctors and nurses using prognostic tools with patients?

Where necessary, prompts will be used to guide the discussion.

24.7.2 SAMPLE QUESTIONS

- I wondered if I could start by asking you a little about your illness / or the illness of your relative/the person you are caring for?

- Can you tell me about some of the reasons why you or your relative or the person you care for decided to or not to take part in the prognostic study?

- Was the decision made following discussion with others around you/them?

- What opinions do you have about the development of a tool/indicator that can estimate the life expectancy of palliative care patients?

- If we could develop a method/tool that is similar or better than a doctors predictions of life expectancy, would you want it?

- Should health professionals check what prognostic information patients/carers desire before initiating prognostic conversations? (Respecting patients/carers information wishes).

- Do you belief that Health Professionals should always share prognostic information with patients to help patients/family carers make decisions and plans? Why/Why not?

- If it is no more accurate than clinicians predictions is it a useful way of starting the conversation with palliative patients/their carers about life expectancy?

- What do you think is the best and most sensitive way to present prognostic information to patients and or relatives/carers? For example, How do you think the tool/indicator should be introduced to patients/relatives/carers? Prompt. Over time, in writing. Via face-to-face conversations.

- Do you think patients/ carers would prefer/find it easier to understand if the prognostic tool/indicator said: Probability 1) A patient/the person you care for have x% probability of surviving for X amount of time OR Length of survival (precise) 2). The patient/the person you care for are predicted to live for this long? (number of days, weeks, months or years) Or Length of survival (vaguer) 3. The outlook for patients like you/the person you care for are Good, Bad, Average?

- Do you think patients would be more comfortable receiving prognostic information in relation to the probability of reaching a significant future event?

- What are your opinions about the usefulness of such a tool/indicator?

- Do you think there are any disadvantages for patients or carers? If yes, can you tell me about what they are?
- Do you think most palliative care patients and their carers want to know this information?

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