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Full Title: The Cost-Effectiveness of Pain Management Strategies in Advanced Cancer

Short title: Cost-Effectiveness of Pain Management

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Abstract

Objectives: Uncontrolled pain in advanced cancer is a common problem and has significant impact on individuals' quality of life and use of healthcare resources. Interventions to help manage pain at the end of life are available but there is limited economic evidence to support their wider implementation. We conducted a case study economic evaluation of two pain self-management interventions (PainCheck and Tackling Cancer Pain Toolkit (TCPT)) compared to usual care.

Methods: We generated a decision-analytic model to facilitate the evaluation. This modelled the survival of individuals at the end of life as they moved through pain severity categories. Intervention effectiveness was based on published meta-analyses results. The evaluation was conducted from the perspective of the UK health service provider and reported cost per quality-adjusted life year (QALY).

Results: PainCheck and TCPT were cheaper (respective incremental costs -GBP148 [-EUR168.53] and -GBP474 [-EUR539.74]) and more effective (respective incremental QALYs of 0.010 and 0.013) than usual care. There was a 65% and 99.5% chance of cost-effectiveness for PainCheck and TCPT, respectively. Results were relatively robust to sensitivity analyses. The most important driver of cost-effectiveness was level of pain reduction (intervention effectiveness). Although cost savings were modest per patient these were considerable when accounting for the number of potential intervention beneficiaries.

Conclusion: Educational and monitoring/feedback interventions have the potential to be cost-effective. Economic evaluations based on estimates of effectiveness from published meta-analyses and using a decision modelling approach can support commissioning decisions and implementation of pain management strategies.

Keywords: cost-effectiveness, palliative care, cancer pain, self-management

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Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

Research ethics and patient consent

As this study did not include primary research with patients or clinicians, ethical approval was not required.

Background

Towards the end of life a significant proportion of cancer patients experience severe pain.(1, 2) A European survey of 5,000 cancer patients found that 72% experienced pain, 90% of which was of moderate-to-severe intensity.(2) Inadequate management of pain at the end of life is likely to have a significant detrimental impact on quality of life (3) and may lead to increased healthcare costs through unplanned hospital visits and admissions.(4) Indeed, one study indicated that poor pain control is the most frequent reason that cancer patients at home need emergency medical help.(5) Clearly, achieving good pain management at the end of life is a priority but service provision in this regard often falls short and interventions that are known to be effective are poorly implemented.

There is growing evidence that self-management strategies facilitated by better communication, pain assessment and patient education can lead to improved pain outcomes.(6, 7) However, economic evidence for these types of interventions is less abundant. Despite the acknowledgement that economic evidence is key to improving access to effective palliative care (8, 9) evaluations are still relatively rare in this context (9, 10) and evaluations in the more specific context of pain at the end of life are rarer still.(11)

We sought to generate evidence on the cost-effectiveness of pain self-management strategies at the end of life by conducting evaluations of case study interventions. Improving the Management of Pain from Advanced Cancer in the Community (IMPACCT) is a UK research programme aimed at the development and testing of interventions for patients at home to facilitate improved pain outcomes through self-management when delivered in addition to routine community palliative care services. The Tackling Cancer Pain Toolkit (TCPT) is a small booklet and DVD containing information on pain and medicines, alongside self-directed learning activities and sources of further information. PainCheck is an internet based pain monitoring system that enables patients to communicate pain data to health professionals routinely. The system alerts professionals when pain scores are above specific thresholds, and allows them to provde feedback through the system or contact patients directly for further assessment.

Primary research evaluating the effectiveness of the IMPACCT interventions is on-going. The aim of the current research was to conduct economic evaluations of PainCheck and TCPT interventions when added to community palliative care delivery to estimate their value for money compared with usual care. The evaluation adopted a decision-analytic modelling approach incorporating published estimates of effectiveness from similar interventions and was designed to inform implementation strategies.

Methods

The economic evaluation followed the NICE reference case (12) and hence was a cost-utility analysis with the primary outcome cost per incremental quality-adjusted life year (QALY) presented from the perspective of the UK healthcare and personal social services provider. The evaluation compared the PainCheck and TCPT pain management strategies in cancer patients at the end of life with usual care in this context. We defined usual care as routine care received by the patients at home from their local community palliative care team as determined by local policies and practices. As part of usual care in the UK, patients at the end of life with specialist needs (for example, poorly controlled pain) should be referred to community palliative care specialists and receive pain treatment and advice as part of that care. While this practice is increasing, services are highly variable across the UK and pain is often managed solely via GPs and community pharmacists. There is no set visit routine as patients access services as and when required but those on strong opiates will typically be reviewed 2-3 times per month, depending on response. During these contacts with health care professionals, response is assessed with pain rating items (such as those in the Numeric Pain Rating Scale) and with less formal questions about pain.

Decision model

We developed a decision-analytic model to facilitate the economic evaluation, an earlier version of which has been previously described.(11) The decision model was a Markov cohort model the structure of which (Figure 1) was informed by patients, clinicians and other published decision models relating to pain. The model is structured around pain health states which are based on accepted 0-10 pain scale cut-offs: 0-4 = No/Mild Pain; 5-6 = Moderate Pain; 7-10 = Severe Pain.(13) More severe pain states are associated with higher costs due to emergency and unplanned healthcare resource use and poorer quality of life. The hypothetical cohort of patients (mean age = 72.4 based on the average age of IMPACCT survey respondents) transited through the model in weekly cycles until dying or until the end of the time horizon (one year). The model parameter values are presented in Table 1 and described below.

Costs

A costing of the IMPACCT interventions is provided in supplementary Table 1. Costs for TCPT related only to printing of the material (one off cost of GBP14.34 [EUR16.33]) and brief telephone contact with a nurse (weekly cost of GBP9.10 [EUR10.36]). Resources required for the provision of PainCheck were larger due mainly to programming requirements. PainCheck

incurred a one-off cost (covering maintenance programming, leaflet printing and nurse time to introduce the tool) of GBP49.01 [EUR55.81] and a weekly cost (covering nurse time for monitoring and patient response) of GBP24.47 [EUR27.86]. Only intervention implementation costs are included and those relating to intervention development are excluded. The health state costs (Table 1) are derived from the IMPACCT patient survey where respondents completed a questionnaire capturing primary and community (e.g. GP visits, nurse contact, etc.) and secondary or hospital (e.g. visits to A&E, hospice stays, etc.) care use in the previous month. Unit costs were obtained from national sources including the PSSRU Costs of Health and Social Care,(14) NHS Reference cost database and the British National Formulary (BNF). All costs are UK pounds and 2017 prices with equivalent Euro values provided in brackets using a historical currency converter (for June 30th 2017).

Health state utility

The utility values for the health states (Table 1) were derived from the IMPACCT patient survey in which respondents completed the EQ-5D-3L measure scored using the UK tariff.(15) We also conducted a sensitivity analysis where utilities were based on the EORTC-8D measure.(16) In view of the fact that the QALY framework has been criticised in palliative care (17), we conducted another analyses based on the ICECAP measure (18) which adopts the capability framework but which may enable cost-utility analyses.

Transition probabilities

Meta-review of educational and monitoring interventions

We conducted a meta-review of educational and feedback/monitoring interventions for improving cancer pain at the end of life. We searched for randomised controlled trials (RCTs) of non-pharmacological interventions in advanced cancer pain and for reviews in this area. We searched Embase Classic and Embase 1947-2017; Ovid MEDLINE(R) 1946-2017; MEDLINE(R) In-Process & Other Non-Indexed Citations. Searches were conducted in February 2017. We short-listed and reviewed those studies reporting a systematic review of either educational or feedback/monitoring interventions for pain. Non-English language publications were excluded. Two researchers reviewed abstracts and differences were resolved by consensus meeting. The shortlisted publications were discussed with a clinician to identify which best reflected the properties of the IMPACCT interventions and hence were suitable proxy estimates of effectiveness. In particular, we were interested in studies of interventions that encouraged self-management (as opposed to having significant levels of

health care professional input). In identifying a suitable review study, we assessed their inclusion criteria to ensure this aligned with the two IMPACCT interventions.

Candidate studies had to report synthesised estimates of effectiveness (and standard error/deviation). Effectiveness had to be based on the Numeric Pain Rating Scale (NPRS)(19). The NPRS is a reliable and valid, self-complete measure of pain. Responses are captured on an 11-point numeric scale ranging from '0' (i.e. “no pain”) to '10' (i.e. “pain as bad as you can imagine”). NPRS questions cover worst intensity, least intensity and average intensity (over the last 24 hours). Our review specifically attempted to identify reports of average pain intensity as this item was also included in the IMPACCT patient survey and was the basis of health state parameters. We also considered RCTs that were published after reviews had been completed.

Effectiveness, pain progression and survival

The initial distribution between the pain severity groups was determined by the IMPACCT patient survey (Table 1). Effectiveness translated into health state transition probabilities by observing the pain category change in the IMPACCT survey respondents following the relevant pain reductions. Intervention effects (rather, a sixth of) were assumed to occur on an incremental basis for six weeks after which pain levels were maintained. In the usual care arm pain was assumed to progress over time. Progression was based on a multinomial regression model predicting change in EQ-5D-3L pain/discomfort item response over time and after controlling for survival in a recent trial including cancer patients at the end of life.(20)

The survival of the cohort was estimated using parametric regression which was fitted to other IMPACCT data. The data (n=4,638; 84% with a cancer diagnosis) was retrospectively collected on all patient referrals to specialist palliative care services in the city of Leeds, UK over 2 years (2012-2014). The sample had a mean survival of 80.77 days (SD=117.81). A number of models were applied to the data including exponential, Weibull and Gompertz. Based on best visual fit with the observed Kaplan-Meier curve and lowest Akaike information criterion (AIC) value, Weibull was selected. As the gamma factor was significant the use of the Weibull model is justified as this indicates a non-constant (and declining) hazard function. The same risk estimates from this analysis were applied to all health states. The survival model estimates were permitted to vary in the probabilistic sensitivity analysis following Cholesky decomposition for correlated regression parameters. During the 52-week model time horizon, 97% of the cohort were expected to have died. Although there is some evidence that

pain can independently explain survival, the evidence is mixed (21) and thus here we assumed they are unrelated.

Analysis

Cost-effectiveness was assessed based on Incremental Cost-Effectiveness Ratio (ICER) and Incremental Net Monetary Benefit (INMB) values. These were generated separately for PainCheck and TCPT in pairwise comparisons versus usual care. A fully incremental analysis was not conducted since these interventions might be used in combination. To test this, a further analysis evaluated receipt of the combined active interventions. The NICE willingness to pay per incremental QALY threshold ([λ] =GBP20,000 [EUR22,774]) was adopted with ICERs below this figure indicating cost-effectiveness. The INMB is a transformation of the ICER where positive INMB values indicate cost-effectiveness; INMB was calculated thus:

$$INMB = (\lambda * \Delta E) - \Delta C$$

A range of one-way, deterministic sensitivity analyses were conducted where alternative model parameter values or assumptions were applied and their impact on cost-effectiveness observed. The deterministic sensitivity analyses tested: basing effectiveness on the upper confidence interval of pain reduction values from meta-analyses (i.e. assuming reduced effect); assuming an additional cost (10% of the cohort receiving a nurse visit) in the PainCheck and TCPT arms; assuming that 50% of those in the PainCheck and TCPT arms experienced pain progression (at usual care rate) after six weeks rather than maintaining pain levels; assuming the starting cohort all had either moderate or severe pain (no mild cases); basing QALY calculations on the EORTC-8D and ICE-CAP; and removing the half cycle correction. We conducted additional analyses exploring the impact of using costs from individual studies identified by the systematic reviews. For PainCheck, a U.S. study was used as an alternative source of intervention costs (22) and for TCPT we used a Dutch study (23); these were chosen from the review as they had relatively large sample sizes, levels of effectiveness similar to the overall mean and as they reported the resources required to deliver the interventions (see **Error! Reference source not found.**).

We also conducted threshold analyses to establish the costs and effectiveness required to achieve cost-effectiveness. We conducted a probabilistic sensitivity analysis (PSA) to characterise overall parameter uncertainty in the model by assigning probability distributions to each of the input parameters, and randomly drawing from these probabilities over the 10,000 Monte Carlo simulations, yielding 10,000 estimates of ICERs and INMB. PSA results were plotted on the cost-effectiveness plane and INMB estimates used to generate the cost-effectiveness acceptability curve (CEAC)(24) The CEAC illustrates the probability that each

intervention would be cost-effective given a range of willingness-to-pay thresholds. Discounting was not required as all costs and benefits were experienced within one year. A half-cycle correction was applied buta sensitivity analysis was also conducted where no half-cycle correction was applied

Finally, we explored the value of further research by conducting a value of information (VoI) analysis which attaches a formal cost to the uncertainty in the cost-effectiveness results.(25) We estimated population level expected value of perfect information (EVPI) which required information on the number of patients who could benefit from the interventions (incidence and number of years the decision is relevant for). According to national data, 149,152 people die each year of cancer in England.(26) Based on European survey results (2) indicating that 72% have pain which in 90% of cases is moderate/severe, yields a relevant annual population of 96,650. We assumed that the decision problem was relevant for 10 years and we discounted values beyond one year based on a 3.5% discount rate. We used the Sheffield Accelerated Value of Information (SAVI) tool(27) to estimate the Expected Value of Perfect Parameter Information (EVPPI) for single parameters. Using the incidence figures we also estimated the budget impact of implementing the interventions over the same period. All analyses were conducted in Stata IC software (version 14; StataCorp) and Excel (Microsoft).

Results

The PRISMA flow diagram for the literature review is included in supplementary material (Supplementary figure 1). Seventeen reviews (Supplementary Table 3) were identified and discussed with the lead clinician. Reviews were not deemed suitable for a number of reasons including: not synthesising study results (e.g.(6, 28)); including non-cancer studies (e.g.(29)); having a restricted population (30); being superseded by more recent reviews (31); or synthesising outcomes from studies investigating interventions comprising a significant element of face-to-face health-care professional delivery(32-34). Results from a review and meta-analysis of pain assessment and feedback interventions was thought a suitable proxy for the effectiveness of PainCheck.(35) The meta-analysis estimated mean reductions in pain ratings of -0.59 (Lower CI =-0.87; Upper CI =-0.3). These figures led to a 0.46 and a 0.39 probability of transiting from Moderate to No/Mild pain and Severe to Moderate pain categories, respectively, over six weeks. The meta-analysis selected as a proxy for TCPT intervention (36) estimated mean reductions in pain ratings of -1.1 (Lower CI =-1.8; Upper CI =-0.41). These figures led to a 0.56 and 0.51 probability of transiting from Moderate to No/Mild pain and Severe to Moderate pain categories, respectively, over six weeks. We could not identify a study that would provide a reasonable approximation of the joint effectiveness of

PainCheck and TCPT thus we made assumption that this was: -1.1 + (-0.59*0.5) or -1.395. We tested this value in the model in a comparison with usual care but included the full costs for both active interventions.

The results from the base case and sensitivity analyses are included in Table 2. PainCheck and TCPT were both cost-saving and more effective than (i.e. they dominated) usual care. However, TCPT led to greater NMB. In general, the incremental costs and benefits were modest. Sensitivity analyses exploring alternative utility values, costs and maintenance of effect after six weeks in most cases did not change the conclusion for either intervention. Only changes to the levels of effectiveness substantively altered the results. Using the upper confidence interval from the respective meta-analyses led to PainCheck no longer being cost-effective while TCPT remained cost-effective. Adopting alternative intervention costs (and effects) from individual studies from within the systematic reviews had the same effect.

Threshold analyses indicated, all else being equal and at current costs, PainCheck requires a pain reduction of at least 0.50 to remain cost-effective; at current levels of effectiveness, PainCheck is cost-effective up to one-off intervention cost of GBP401.86 [EUR457.59] or weekly intervention costs of GBP58.25 [EUR66.33] being incurred. At current costs TCPT requires a pain reduction of at least 0.40 to remain cost-effective; at current levels of effectiveness TCPT is cost-effective up to one-off intervention costs of GBP744.61 [EUR847.88] or weekly intervention costs of GBP43.44 [EUR49.46] being incurred. The combined intervention was cost-effective but represented less value for money than TCPT alone.

The probabilistic results yielded similar results to those from the deterministic analyses although INMB is reduced. A higher number of simulations in the TCPT arm were cost-saving vs. usual care than is the case with PainCheck. In both comparisons, all simulations showed positive QALY gain over usual care. The cost-effectiveness planes (Figure 2) indicates the spread of ICERs from the Monte Carlo simulations, representing parameter uncertainty. The cost-effectiveness acceptability curves (Supplementary Figure 2) indicate that PainCheck has a 65% chance of being the cost-effective option and TCPT a 99.5% chance of being cost-effective at a willingness to pay threshold of GBP20,000 [EUR22,774] per QALY.

For PainCheck, the population EVPI per year was GBP2,945,026 [EUR3,353,460] and GBP24,592,210 [EUR28,002,805] over 10 years indicating a significant cost of uncertainty in the decision. Given that TCPT was highly likely to be cost-effective, the population EVPI was low (GBP10,464 [EUR11,915] per year) indicating further research on the topic may be unnecessary. The EVPPI figures for TCPT were effectively zero given the lack of uncertainty in the decision. They were also zero for PainCheck parameters except for the severe and

moderate pain health state costs. The cost of decisional uncertainty surrounding the moderate health state cost was GBP971,100 [EUR1,105,778] over ten years. This was much higher for the severe health state cost parameter (GBP15,590,000 [EUR17,752,115]) and the magnitude suggests additional research into the cost of cancer pain may be warranted. The budget impact estimates indicate that PainCheck would lead to savings of GBP663,831 [EUR755,895] per year or GBP5,543,272 [EUR6,312,046] over 10 years. The estimated cost savings for TCPT were estimated to be GBP23,369,253 [EUR26,610,241] per year and GBP195,143,121 [EUR222,206,740] over 10 years.

Discussion

These analyses represent the most comprehensive assessment to date of the value for money of pain management interventions at the end of life. Using a decision modelling approach, we compared two types of intervention (educational and pain monitoring/feedback) against usual care from the perspective of the health and social care provider. We relied on estimates of effectiveness from published meta-analyses. PainCheck and TCPT are relatively inexpensive and the evaluations suggest that both have the potential to be cost-effective. Indeed, in the base case analyses, both interventions were cheaper and more effective than usual care. The conclusions were relatively robust to a number of sensitivity analyses. The effectiveness parameter appeared relatively more influential in determining cost-effectiveness than intervention costs or utility values. Assuming all patients were either in moderate or severe pain improved the benefit of the IMPACCT interventions noticeably. A scenario where both interventions were received would be a worse strategy than implementing TCPT alone, mainly due to the additional costs of PainCheck. However, assumptions were made here on the level of combined effect.

Although the use of the generic QALY framework (based on EQ-5D) to evaluate palliative care interventions has been questioned (17), here the use of condition specific QALY (EORTC-8D) and capability-based approaches (ICE-CAP) yielded reduced incremental benefits for the active interventions. It is possible that the EQ-5D fails to capture additional benefits this patient group may experience following improved pain management such as a greater feeling of control and the emotional positives that come with being able to stay at home. However, the EQ-5D appears adept at discriminating between people based on pain level and this may explain the relative performance of the utility measures as the decision-model is predicated on pain categories.

The probabilistic analyses suggest that both PainCheck and TCPT are highly likely to deliver QALY gains over usual care. However, in both cases, the interventions were less likely to lead

to cost-savings. Incorporating parameter uncertainty in the model suggests that PainCheck and TCPT have 65% and 99.5% chance of being cost-effective, respectively. The greater uncertainty surrounding PainCheck relates to the higher cost and lower assumed effect. The Value of Information analysis suggest that additional research on PainCheck is warranted and the EVPPI values indicate that reducing uncertainty surrounding cost estimates should be a focus.

The costs predicted here are similar although lower than those presented in a recent publication.(37) However, we used a different definition of end of life and much lower survival periods. Although the cost savings associated with each intervention were modest, values for the estimated population are potentially substantial (GBP5,543,272 [EUR6,312,046] and GBP195,143,121 [EUR222,206,740] over 10 years for PainCheck and TCPT, respectively).

Limitations

We did not have direct estimates of the effectiveness of either active case study interventions evaluated here and relied on synthesised estimates from meta-analyses. While the studies employed in the analyses as the basis of effectiveness estimates were selected following a meta-review and due consideration, it is possible that these reviews incorporate studies that are not accurate reflections of the PainCheck and TCPT interventions. It is possible that these reviews and synthesised outcomes derive from disparate study interventions or designs which may have biased results. Adam and colleagues(35), reviewing patient feedback/monitoring studies, found most were prone to some element of bias and that two studies contributing to the synthesis should be treated with caution. As the effectiveness estimates in those two studies were above the mean, their exclusion would reduce the assumed overall effectiveness (albeit slightly given study weightings) for PainCheck. While there were very few reviews relating to patient feedback/monitoring, there were several targeting educational interventions. The review by Bennett and colleagues was selected based on appropriateness of their study inclusion criteria. There is limited information in the review of the quality of studies included and potential for bias. Examination of study outcomes indicates the presence of significant heterogeneity with one outlier study reporting a very large intervention effect and this may have biased results. However, it is worth pointing out that the uncertainty in outcome should be captured in the probabilistic sensitivity analyses presented here. Furthermore, excluding that study from the weighted mean still yielded an effect greater than that required (-0.40) for TCPT to be cost-effective. Although, of course, this is based on the use of costs estimated here for the TCPT intervention. It is also possible that there may be individual randomised controlled trials that better reflect the potential effect of either active intervention.

Although it has been suggested that informal care costs are an important consideration in palliative care economic evaluations (38) we did not include these in the current analyses. We wished to adhere to the NICE reference case which excludes these costs but, more importantly, we did not have health state data relating to informal care costs. It is likely that carers of patients in higher pain categories incur higher costs; thus, adopting a broader perspective and including informal care costs would likely increase the estimates of value for money for PainCheck and TCPT. However, increased self-management may also increase informal care requirements and further research is needed to explore this.

Further research and implications

The decision model generated and tested here is robust and may be a tool that, following adaptations, has other useful applications in this palliative care. It may also be useful for local decision makers considering commissioning alternative pain management strategies. The active interventions evaluated here have the potential to be cost-effective and additional research, for example, in the form of randomised trials or observational data collection and analysis, may be warranted to add to the evidence base.

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Table 1: Model parameter values

Parameter	Mean	SE	Distribution∞	Source
Intervention costs				See supplementary Table 1
One-off cost for TCPT	GBP14.34 [EUR16.33]	N/A – Fixed	N/A - Fixed	
Weekly cost for TCPT	GBP9.10 [EUR10.36]	N/A – Fixed	N/A - Fixed	
One-off cost for PainCheck	GBP49.01 [EUR55.81]	N/A – Fixed	N/A - Fixed	
Weekly cost for PainCheck	GBP24.27 [EUR27.86]	N/A – Fixed	N/A - Fixed	
Health state costs (weekly)*	B			IMPACCT Patient survey (39)
Constant (base= No/Mild Pain)	GBP553.59 [EUR630.37]	GBP105.78 [EUR120.45]	Lognormal	
Moderate Pain	GBP160.34 [EUR182.58]	GBP160.49 [EUR182.75]	Lognormal	
Severe Pain	GBP341.54 [EUR388.91]	GBP203.93 [EUR232.21]	Lognormal	
Health state utility**	β			EQ-5D - IMPACCT Patient survey (39)
Constant (base= No/Mild Pain)	0.525	0.029	Beta	
Moderate Pain	-0.102	0.045	Gamma (decrement)	
Severe Pain	-0.377	0.047	Gamma (decrement)	
Starting proportions				IMPACCT Patient survey (39)
No/Mild pain	0.439	0.031	Dirichlet - Gamma	
Moderate pain	0.305	0.030	Dirichlet - Gamma	
Severe pain	0.256	0.028	Dirichlet - Gamma	
Intervention effectiveness***				
Standard care	0.0	N/A - Fixed	N/A - Fixed	Assumption
PainCheck	-0.59	0.143	BetaΔ	(35)
Tackling Cancer Pain toolkit	-1.1	0.357	BetaΔ	(36)
Pain progression****				(20)
No/Mild pain to Moderate pain	0.004	0.002	Beta	
No/Mild pain to Severe pain	0.002	0.001	Beta	
Moderate pain to Severe pain	0.002	0.001	Beta	
Survival – Weibull parametric model*****				Palliative Care Referral Data(40)
Gamma (_ln/p)	-0.306	0.011	N/A^	
Constant	-2.019	0.083		
Age	0.005	0.001		

∞Distributions used in the probabilistic sensitivity analysis; ∆Pain reductions are first converted to probabilities based on likelihood of pain category change in IMPACCT survey respondents;^Uses estimates based on the regression covariance matrix; *Derived using generalised linear model (Gamma family, Log link); **derived using ordinary least squares regression; ***Change in pain rating scale vs. usual care;****Weekly probability applied only to standard care arm, all other transition probabilities assumed to be 0.0; *****Weekly mortality following referral to palliative care

Table 2: Cost-effectiveness results

Analysis	Total Cost	Total QALY	Incr. Cost	Incr. QALY	ICER (vs. Usual care)	INMB
Base case Analysis - deterministic						
PainCheck	GBP7,532 [EUR8,577]	0.090	-GBP148 [-EUR169]	0.010	Dominates UC	GBP354 [EUR403]
TCPT	GBP7,207 [EUR8,207]	0.093	-GBP474 [-EUR540]	0.013	Dominates UC	GBP731 [EUR832]
Usual Care	GBP7,680 [EUR8,745]	0.080	--	--	--	--
Base case Analysis - probabilistic						
PainCheck	GBP7,691 [EUR8,758]	0.088	-GBP7 [-EUR8]	0.008	Dominates UC	GBP160 [EUR182]
TCPT	GBP7,401 [EUR8,427]	0.089	-GBP297 [-EUR338]	0.009	Dominates UC	GBP477 [EUR543]
Usual Care	GBP7,698 [EUR8,766]	0.080	--	--	--	--
Combined interventions						
PainCheck+TCPT	GBP7,500 [EUR8,540]	0.093	-GBP181 [-EUR206]	0.013	Dominates UC	GBP440 [EUR501]
Sensitivity analyses						
Upper CI for effectiveness						
PainCheck (-0.30)	--	--	GBP268 [EUR305]	0.002	GBP109,235 [EUR124,384]	-GBP219 [EUR249]
TCPT (-0.41)	--	--	GBP44 [EUR50]	0.003	GBP15,465 [EUR17,610]	GBP13 [EUR15]
Assuming 10% receive nurse visit						
PainCheck	--	--	-GBP143 [-EUR163]	0.010	Dominates UC	GBP349 [EUR397]
TCPT	--	--	-GBP469 [-EUR534]	0.013	Dominates UC	GBP727 [EUR827]
Adopting intervention costs from other studies						
PainCheck			GBP274 [EUR312]	0.010	GBP26,631 [EUR30,324]	-GBP68 [-EUR77]
TCPT			-GBP362 [-EUR412]	0.013	Dominates UC	GBP620 [EUR706]
Adopting intervention costs and effectiveness from other studies						
PainCheck			GBP259 [EUR295]	0.010	GBP24,755 [EUR28,188]	-GBP50 [-EUR57]

TCPT			-GBP243 [-EUR277]	0.010	Dominates UC	GBP453 [EUR516]
50% pain progression >6 weeks for PainCheck/TCPT						
PainCheck	--	--	-GBP108 [-EUR122.98]	0.010	Dominates UC	GBP300 [EUR342]
TCPT	--	--	-GBP430 [-EUR489.63]	0.012	Dominates UC	GBP673 [EUR766]
Patients begin in moderate or Severe pain (50:50)						
PainCheck	--	--	-GBP394 [-EUR449]	0.016	Dominates UC	GBP710 [EUR808]
TCPT	--	--	-GBP819 [-EUR933]	0.020	Dominates UC	GBP1,228 [EUR1,398]
Using EORTC-8D Utilities						
PainCheck	--	--	-GBP148 [-EUR169]	0.004	Dominates UC	GBP233 [EUR265]
TCPT	--	--	-GBP474 [-EUR540]	0.005	Dominates UC	GBP579 [EUR659]
Using ICE-CAP Utilities						
PainCheck	--	--	-GBP148 [-EUR169]	0.004	Dominates UC	GBP228 [EUR260]
TCPT	--	--	-GBP474 [-EUR540]	0.005	Dominates UC	GBP573 [EUR652]
No half-cycle correction						
PainCheck	--	--	-GBP143 [-EUR163]	0.010	Dominates UC	GBP348 [EUR396]
TCPT	--	--	-GBP468 [-EUR533]	0.013	Dominates UC	GBP725 [EUR826]

Figure 1: Decision model structure

Figure 2: Cost-effectiveness planes

Supplementary figure 1: PRISMA diagram

Supplementary figure 2: CEACs