ORIGINAL REPORT: ECONOMIC RESEARCH

DEEP Study: Modeling Outcomes and Costs of Persistent Orofacial Pain

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Abstract: *Persistent orofacial pain (POFP) affects patients' daily lives and can lead to significant costs for them and/or the health service provider. This partial economic evaluation examined costs and utilities experienced by individuals with POFP over a 24-mo period and used these data to populate the life course Markov model used to estimate costs and quality-adjusted life years (QALYs) from pain onset over an individual's life course while receiving usual health care. A total of 202 people receiving care for POFP were followed for 24 mo. Data were collected every 6 mo on pain-related disability (Graded Chronic Pain Scale dichotomized to low [0–IIa] or high [IIb–IV] pain-related disability states), health service utilization, and health-related quality of life measured by QALYs derived from the EQ-5D-5L. Unbalanced regressions were used to demonstrate how costs and QALYs varied according to participant characteristics with the results used to parameterize a Markov model. This probabilistic Markov model was used to estimate the outcomes for a cohort of POFP patients from age 25 y until death as determined by age- and sex-specific mortality rates. Across all time points, complete data were available from 129 participants. A high pain-related disability state led to significantly increased health care cost (£221; 95% confidence interval [CI], 87–355; P < 0.01) and a significant decrease in quality of life (mean difference, –0.08; 95% CI, –0.11 to –0.05; P < 0.0001) over a 24-mo period. The Markov model estimated that the average cost was £27,317 (95% CI, 26,558–28,046) and the average lifetime QALYs were 17.54 (95% CI, 17.38–17.71). The modeling suggests that a cohort of POFP patients from age 25 y would only accrue 18 QALYs per person before death. POFP therefore exerts a considerable impact on health, and it is likely more effective care (pathways) could realize substantial gains in terms of both treatment outcomes and health care utilization.*

Knowledge of Transfer Statement: *Despite a substantial number of consultations, individuals experiencing the care pathways in this study continued to have far from perfect health over their life course. The modeling suggests they would only experience 18 y in "perfect health." There is considerable scope to improve current care/outcomes and patient experience.*

Keywords: chronic pain, facial pain, health care utilization, cost analysis, Graded Chronic Pain Scale, temporomandibular joint disorders

Introduction

Persistent orofacial pain (POFP) refers to a group of conditions that affect up to 1 in 15 of the population by producing pain in the mouth and/or face (Aggarwal et al. 2010). The group of conditions includes the following disorders known by varying names: temporomandibular disorders (TMDs), atypical odontalgia/persistent dentoalveolar pain disorder/posttraumatic trigeminal neuropathic pain, burning mouth syndrome, trigeminal neuralgia, and persistent idiopathic facial pain/atypical facial pain (Zakrzewska 2013). POFP causes similar impacts on oral health–related quality of life to symptomatic apical periodontitis (Shueb et al. 2015), and in generic health status (measured by EQ-5D-5L [see Appendix]), its impacts are of comparable magnitude to those of arthritis and depression (Durham et al. 2015).

Given POFP's impacts on quality of life, it is unsurprising that those living

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A supplemental appendix to this article is available online.

with POFP seek health care to help alleviate its impacts (Breckons et al. 2017). Care provided for POFP should be multidisciplinary and holistic, with an aim to decrease pain-related disability, thereby improving quality of life (Zakrzewska 2013). There are suggestions in the literature, however, that care pathways for POFP (Durham et al. 2013; Durham et al. 2016; Breckons et al. 2017; Lövgren et al. 2017) are problematic, with patients struggling to obtain a diagnosis/assessment or management at their first or subsequent contacts with health care professionals. The DEEP Study (Developing Effective and Efficient Care Pathways in Persistent Pain) (Durham et al. 2014) provides corroborative data from this perspective and also demonstrates the importance of pain-related disability in determining the impact of POFP on individuals' everyday lives and their use of health care services (Durham et al. 2016; Breckons et al. 2018).

It is, however, currently uncertain how routine care for POFP, with its resultant costs and outcomes, changes pain-related disability over the life course of the patient, thereby providing benefits in terms of improvements in quality of life. To help estimate this, it is possible to determine norm-referenced preference values known as utilities for each pain-related disability state to reflect the quality of life experienced while in that state and the costs of each state (Durham et al. 2015; Durham et al. 2016). These data can then be used to model and estimate the number of quality-adjusted life years (QALYs; with 1 QALY being equal to 1 y of life in perfect health; NICE 2018) associated with health care provided for POFP. It is also possible to model and estimate the cumulative cost for the number of QALYs.

This modeling is important as for the first time it will provide an estimate of "usual" treatment's efficacy using a lifetime horizon, thereby providing a baseline for comparison to other health care systems or modifications to care pathways. The aim of this study was, therefore, to examine the costs and utilities experienced by individuals with POFP over a 24-mo period and use these data to populate the life course Markov model used to estimate costs and QALYs from pain onset over an individual's life course while receiving current, usual health care for their condition.

Methods

Ethical approval for the DEEP Study was received from the NHS National Research Ethics Service (NRES Reference: 12/YH/0338). Its protocol was published a priori and is available on open access (Durham et al. 2014), as are its previous publications (Durham et al. 2015; Durham et al. 2016; Breckons et al. 2017; Breckons et al. 2018). The protocol and previous articles explain the study's generic methods in detail. A brief summary of these methods is provided in this article, followed by the specific details on the methods used for the current analysis and for the development of the model. The study represents a partial economic evaluation as it is based on a longitudinal cohort (Drummond et al. 2015). The data from this cohort are used to estimate costs and QALYs. As it is a longitudinal cohort, the present report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, and as a partial economic evaluation (Drummond et al. 2015), it also addresses the relevant points of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Sample and Recruitment

A sample size of 200 patients with POFP was determined to be needed in order to detect a difference between groups (primary and secondary care) at a moderate effect size of 0.4 (2-tailed) and allow regression examining up to 30 predictors of cost ($\alpha = 0.05$; $\beta = 0.8$) (Green 1991). A priori, a measure of pain-related disability (dichotomized graded chronic pain status) was set as the predictor of interest given it has prognostic predictive value and also helps stratify treatment (Von Korff et al. 1992; Manfredini et al. 2013; Kotiranta et al. 2015). The recruitment target for the study was set at 240 individuals from both community practices (nonspecialist general medical [$n = 25$] and dental [$n = 10$]) and specialist practice (hospital: neurology, oral and maxillofacial surgery, oral medicine, and restorative dentistry) settings in the Northeast of England. This target allowed for a 20% attrition rate through nonresponse and loss to follow-up. Individuals were eligible to participate if they

- Had experienced POFP for ≥3 mo and were ≥18 y of age
- Screened positive using a validated self-report instrument for having pain of a musculoskeletal (sensitivity 63.1%; specificity 85.9%) and/or neuropathic or neurovascular origin (sensitivity, 66.3%; specificity, 96.8%) (Durham et al. 2016)
- Were able to communicate and understand complex constructs in English and thereby also give informed consent

If a specialist diagnosis was available that contradicted the results of the screening instrument, the individual was invited to participate in the study and the specialist's diagnosis used to assign the relevant origin of pain to their unique study identifier. All those recruited then progressed with the care and the care pathways they were currently on (i.e., no interventions were made by the study team with respect to their diagnosis, treatment, or current care pathway).

Measures and Instruments

Trained interviewers captured participants' sociodemographic and socioeconomic characteristics at baseline using a case report form. Participants then went on to complete a total of 7 instruments at regular periods over the course of the study (Durham et al. 2014; Durham et al. 2016) with 3 of these instruments being relevant to the present analysis: EQ-5D-5L, Graded Chronic Pain Scale [GCPS], and the Use of Services and Productivity Questionnaire (USPQ; Von Korff et al. 1992; Wordsworth and Thompson 2001; Herdman et al. 2011).

These 3 instruments were completed every 6 mo over a 24-mo period by participants, and full details of their scoring are within the Appendix and a previous publication (Durham et al. 2016). Only visits related to the orofacial pain condition were counted within the USPQ.

EQ-5D-5L is a generic health-related preference-based measure consisting of 5 items that examine mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 items is ranked from 1 (*no problems*) to 5 (*severe problems*), and the 5 rankings are concatenated to produce a score for that health state. It is sensitive to the impacts of POFP (Durham et al. 2015) and produces utilities for each health state it defines between 11111, which is for best health state, and 55555, which is the worst possible health state. These utilities range from 1 ("perfect" health for the best health state) through to −0.59 (worst possible state of health) and are derived from a representative sample of the UK population (Janssen and Szende 2014).

Data Analysis

All data were cross-checked and cleaned prior to analysis by 2 researchers (JD and MB). All costs were initially calculated in pounds sterling at 2012 prices (the year the study started) and subsequently converted to 2020 prices (the most recent data available) using the Consumer Price Index (CPI) (Breckons et al. 2018; ONS 2020). The mean UK exchange rate to US dollars in 2020 was UK £1.00 = US $1.28, and it is possible to convert the costs in this article to any other currency using the Campbell and Cochrane Economics Methods Group (CCEMG) and Evidence for Policy and Practice Information and Coordinating Centre's (EPPI-centre) Cost Converter (Shemilt et al. 2010; CCEMG-EPPI-centre 2020).

A detailed explanation of the estimation of the unit costs from the varying sources used (NHS 2005; Curtis 2012; Department of Health 2012; Joint Formulary Committee 2012; HSCIC 2014) is provided elsewhere (Durham et al. 2016). All unit costs were multiplied against the appropriate data gathered from the USPQ to create the cost for that particular utilization of health care—for example, number of general medical practitioner attendance multiplied against unit cost of general medical practitioner attendance to calculate total cost for general medical practitioner attendance. All health care utilization costs for each individual were summed to create a total health care utilization cost at each time point for each individual. This total cost for the time point related to the *preceding* 6-mo period.

The initial phase of analysis used STATA version 13 (StataCorp LP) in order to calculate descriptive statistics, examine distributions, and provide bootstrapped confidence intervals around point estimates of the total cost at each time point. Best practice for managing cost data was followed throughout the analysis (Barber and Thompson 2004; Mihaylova et al. 2011). Missing data were infrequent with a mean level of missing data between 2% and 6% across the time points. Missing data were imputed according to standardized guidance for the relevant instrument. Missing cost data were imputed using UK reference cost data and/or median/mean imputation where appropriate. Missing USPQ data were managed by assuming nonapplicable when questions were left completely blank with a zero value employed, using mean imputation at an item level when questions were partially completed (e.g., respondents indicating they had incurred a cost but did not provide the cost value). Worked examples of this are freely available in a previous publication's appendix (Breckons et al. 2018).

Model Design

A cohort Markov model was constructed in order to examine the cost and QALYs accrued over the life course of an individual with POFP under the current care pathway. Total costs per modeled patient (£) were calculated at 2020 prices and discounted at 3.5%, as were utilities (NICE 2020) (Fig. 1). In addition, sensitivity analyses were conducted for 0%, 5%, and 10% discount rates, and these data are available in the Appendix. The perspective taken was the United Kingdom's National Health Service (NHS).

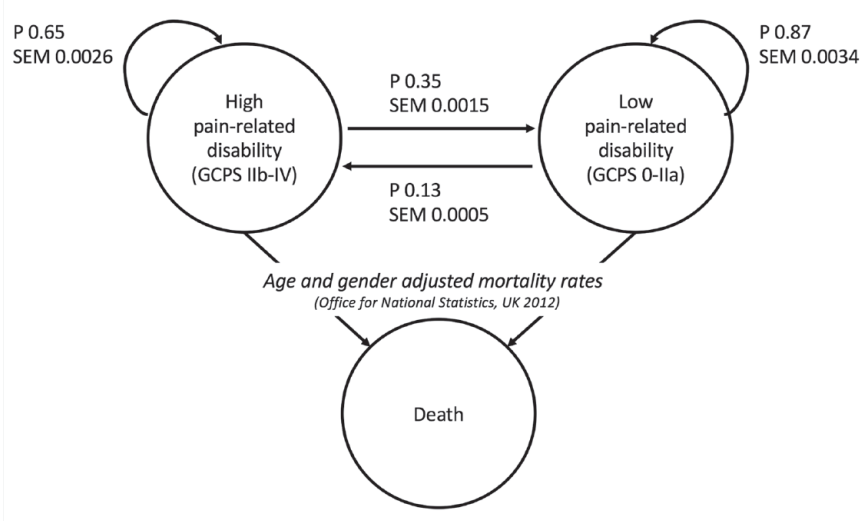
Population and treatment options

The cohort modeled included females with a starting age of 25 y, who were selected as data suggest that those in the age group from 18 to 35 y more frequently experience first-onset POFP, and females are up to 4 times more frequently affected by with POFP and therefore seek health care more frequently than males (Aggarwal et al. 2010; Rollman et al. 2012). Mortality was defined by age-specific mortality rates for England and was applied irrespective of health state related to POFP. All women modeled were assumed to have died before the age of 100 y. Due to the paucity of the evidence base for management of POFP (Al-Baghdadi et al. 2014; Haggman-Henrikson et al. 2017), there were no specific treatment options specified for the model. Instead, the model examined the movement between different health states: low and high pain-related disability.

Model structure and definition of health states

Due to robust data demonstrating the importance of pain-related disability in predicting health care utilization, prognosis, and outcome (Durham et al. 2016; Breckons et al. 2018), we elected to use 2 health states in addition to mortality. These 2 states were low pain-related disability and high pain-related disability, which were defined by the dichotomized GCPS. Within the low state, it is possible to have zero pain(-related) disability as well as some (intermittent) lower levels of pain, and this was felt to be more realistic given current management strategies (i.e., that a low state could also include full remission, low levels of pain-related disability, or recurrent low level pain-related interference). The dichotomizing of the GCPS is consistent with the findings of the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study, which examined incident and chronic cases of TMD (Ohrbach et al. 2011; Slade et al. 2013).

Figure 1. Markov model for estimation of total cost and quality-adjusted life year gain with current care pathway. GCPS, Graded Chronic Pain Scale; P, probability of transition; SEM, standard error of the mean of the probability.



The cycle length of the model was set at 6 mo as clinical change due to intervention(s) would be expected within this time frame (Moufti 2007). In total, 150 cycles were used producing the same number of data sets. The model was run for 1,000 iterations (with each iteration being a hypothetical patient). An initial distribution of 62% of the cohort starting in the low pain-related disability state was assigned given this was the proportion of those in a low state at baseline. Sensitivity analyses were also conducted at higher percentages starting in the low pain-related disability state. The model was constructed and run within TreeAge Pro 2018 (TreeAge Software).

Data Sources

Utility values and costs

Unbalanced regression models using the data from all time points were used to determine the point estimates, standard errors, and confidence intervals (CIs) that were used to populate the Markov model. Informed by best practice in handling cost and utility data (Barber and Thompson 2004; Mihaylova et al. 2011), the regressions used were a generalized estimating equation (GEE) model using an identity link function and a gamma family for total health care utilization cost, as well as a generalized least squares (GLS) random-effects model for utilities. Both models were controlled for age, sex, socioeconomic status, and origin and duration of pain.

Probabilities

The probabilities for transitioning between or staying within the low and high pain-related disability states were calculated from the longitudinal data available on individuals within the DEEP Study. The frequency of all transitions available (n = 592) over the 24-mo period was pooled and the probabilities of a 2-by-2 matrix then calculated for either staying in the current state or moving to a different state (Fig. 1).

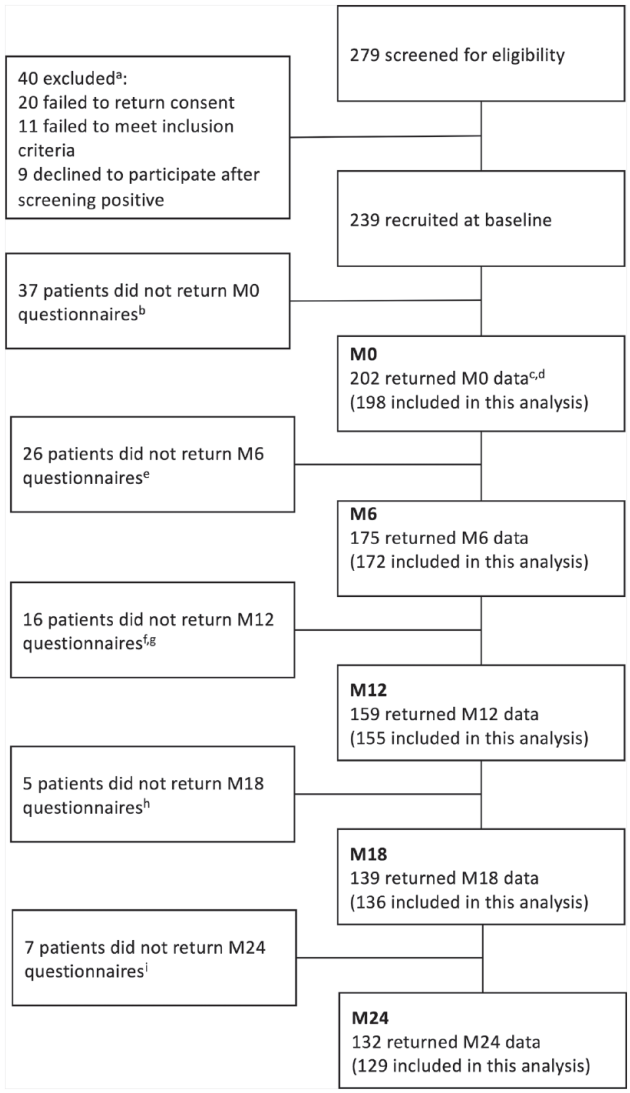
Probabilistic Sensitivity Analysis

The Monte Carlo simulation was used to test the effect of uncertainty in parameter estimates. For the Monte Carlo simulation, 1,000 iterations were run. For each iteration, the simulation selects values for each parameter in the model (cost and utility) according to a distribution around each parameter. Visual inspection of the distribution of the cost and utility data informed the choice of distribution for the parameter within the model: beta distribution for utilities and gamma for costs. The limits of uncertainty were based on 95% CIs around the point estimates calculated from the unbalanced regression models and pooled transition frequency data. Half-cycle corrections were made.

Results

In total, 387 individuals were referred to the study as potentially eligible for inclusion, with 279 agreeing to be screened. Of these, 268 of those screened met the inclusion criteria, and 239 agreed to participate. The flow of participants through the study is shown in Figure 2. Participants were included in the current analysis if they had USPQ and GCPS data at the relevant time points. Table 1 demonstrates the socioeconomic and sociodemographic status of the sample alongside their pain-related disability. Most of the sample were educated (80% holding at least public exams from age 16 y) and in some form of employment (59%). Their homes were predominantly within areas categorized as more deprived (59% of sample lived in areas categorized in the bottom half of England's deprivation index, the index of multiple deprivation [IMD], which measures seven distinct domains in order to generate a composite global score. The domains are: Income Deprivation, Employment Deprivation, Health

Figure 2. CONSORT diagram demonstrating patient flow over course of study. Diagram demonstrates overall dropout from the study at each time point and also indicates the number of people included in this analysis (i.e., people returning both Graded Chronic Pain Scale and Use of Services and Productivity Questionnaire).



[a]There was no significant difference in age, sex, or origin of pain between positively screened patients who participated and those who declined ($P > 0.05$).
[b]There were no significant differences in sex, ethnicity, duration of pain, or origin of pain between those dropping out and the 198 participants whose data were included in the study ($P > 0.05$). However, those participating were significantly older than those who dropped out ($P < 0.01$).
[c]One patient withdrew from the study at M18 and requested that their data be withdrawn.
[d]Data were not received from 3 participants at M0 who reported returning data, but this was not received by the study team. These patients returned data at subsequent time points.
[e]There was no significant difference between those dropping out at M6 and the M0 sample on the basis of age, sex, ethnicity, duration of pain, or origin of pain ($P > 0.05$).
[f]There was no significant difference between those dropping out at M12 and the M0 sample on the basis of age, sex, ethnicity, or origin of pain ($P > 0.05$), although those dropping out had a significantly longer duration of pain than those participating at baseline ($P < 0.05$).
[g]One of these patients went on to complete data at a further time point.
[h]There was no significant difference between those dropping out at M18 and the M0 sample on the basis of age, sex, duration of pain, or origin of pain ($P > 0.05$), although those dropping out consisted of a greater proportion of a White British ethnic group than those participating at baseline ($P < 0.01$).
[i]There was no significant difference between those dropping out at M24 and the M0 sample on the basis of age, sex, duration of pain, or origin of pain ($P > 0.05$), although those dropping out consisted of a greater proportion of a White British ethnic group than those participating at baseline ($P < 0.01$).

Table 1.
Sociodemographic and Socioeconomic Status and Levels of Pain-Related Disability of Sample.

Characteristic	Time Point				
	M0 (*n* = 198)	M6 (*n* = 172)	M12 (*n* = 155)	M18 (*n* = 136)	M24 (*n* = 129)
Age and sex					
Age, mean (SD), y	51.9 (16)	52.3 (15.6)	53.1 (15.2)	53.4 (14.8)	53.9 (14.8)
Females, *n* (%)	160 (80.8)	140 (81.4)	128 (82.6)	113 (83.1)	107 (82.9)
Ethnic origin, *n* (%)					
White	159 (80.3)	138 (80.3)	122 (78.7)	104 (76.5)	100 (77.5)
Black	1 (0.5)	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.8)
Other, Chinese	1 (0.5)	1 (0.6)	1 (0.7)	1 (0.7)	0 (0)
Other, not known	4 (2.0)	3 (1.7)	3 (1.9)	3 (2.2)	3 (2.3)
Not provided	7 (3.5)	6 (3.5)	5 (3.2)	5 (3.7)	4 (3.1)
Missing data	26 (13.0)	23 (13.4)	23 (14.8)	22 (16.2)	21 (16.3)
Highest educational level, *n* (%)					
University[a]	76 (38.3)	67 (38.9)	61 (39.4)	54 (39.7)	52 (40.3)
Vocational qualifications	43 (21.7)	38 (22.1)	35 (22.6)	28 (20.6)	29 (22.5)
Secondary school public examinations	39 (19.7)	33 (19.2)	26 (16.8)	24 (17.6)	22 (17.1)
No public examinations	23 (11.6)	19 (11.1)	18 (11.6)	16 (11.8)	14 (10.9)
Missing data	17 (8.6)	15 (8.7)	15 (9.7)	14 (10.3)	12 (9.3)
IMD decile ranking of home postcode, *n* (%)[b]					
9 and 10 (least deprived)	29 (14.7)	23 (13.4)	16 (10.3)	15 (11.0)	14 (10.9)
7 and 8	39 (19.7)	31 (18.0)	26 (16.8)	26 (19.1)	26 (20.2)
5 and 6	31 (15.7)	30 (17.5)	29 (18.7)	24 (17.7)	22 (17.1)
3 and 4	44 (22.2)	39 (22.7)	37 (23.9)	32 (23.5)	30 (23.3)
1 and 2 (most deprived)	52 (26.3)	48 (27.9)	45 (29.3)	37 (27.2)	36 (27.9)
Missing data	3 (1.5)	1 (0.6)	2 (1.3)	2 (1.5)	1 (0.8)
Employment,[c] *n* (%)					
Groups 1–3	59 (29.8)	54 (31.4)	52 (33.6)	45 (33.1)	46 (35.7)
Groups 4–6	39 (19.7)	35 (20.4)	26 (16.8)	23 (17)	22 (17.1)
Groups 7–9	18 (9.1)	17 (9.9)	17 (11)	15 (11.1)	13 (10.1)
Unemployed	27 (13.7)	22 (12.8)	19 (12.3)	15 (11.1)	13 (10.1)
Retired	44 (22.3)	35 (20.4)	33 (21.3)	32 (23.6)	29 (22.5)
Sick leave due to POFP	2 (1.1)	2 (1.2)	2 (1.3)	2 (1.5)	2 (1.6)
Student	5 (2.6)	3 (1.8)	2 (1.3)	2 (1.5)	2 (1.6)
Missing data	4 (2.1)	4 (2.4)	4 (2.6)	2 (1.5)	2 (1.6)

(continued)

Table 1.
(continued)

Characteristic	Time Point				
	M0 (*n* = 198)	M6 (*n* = 172)	M12 (*n* = 155)	M18 (*n* = 136)	M24 (*n* = 129)
Origin of pain, *n* (%)					
MSK	86 (43.5)	77 (44.8)	72 (46.5)	64 (47.1)	60 (45.5)
NP/NV	64 (32.4)	55 (32.0)	49 (31.7)	42 (30.9)	42 (31.9)
COMB	48 (24.3)	40 (23.3)	34 (21.9)	30 (22.1)	30 (22.8)
GCPS grade, *n* (%)					
Low pain[d]	121 (61.1)	112 (65.2)	113 (73.1)	97 (71.5)	94 (73)
0	3 (1.5)	7 (4.1)	7 (4.6)	7 (5.2)	6 (4.7)
I	61 (30.8)	72 (41.9)	80 (51.7)	66 (48.6)	69 (53.5)
IIa	57 (28.8)	33 (19.2)	26 (16.8)	24 (17.7)	19 (14.8)
High pain[d]	77 (38.9)	60 (35.1)	42 (27.3)	39 (28.8)	35 (27.3)
IIb	35 (17.7)	29 (16.9)	20 (13)	18 (13.3)	18 (14)
III	31 (15.7)	26 (15.2)	13 (8.4)	14 (10.3)	10 (7.8)
IV	11 (5.6)	5 (2.9)	9 (5.9)	7 (5.2)	7 (5.5)

COMB, combined origin; GCPS, Graded Chronic Pain Scale status; IMD, index of multiple deprivation, English Government; MSK, musculoskeletal; Mx, month of data collection; NP/NV, neuropathic/vascular; POFP, persistent orofacial pain.
[a]Undergraduate or postgraduate degree or diploma.
[b]The index of multiple deprivation [IMD] measures seven distinct domains in order to generate a composite global score: Income Deprivation, Employment Deprivation, Health Deprivation and Disability, Education Skills and Training Deprivation, Barriers to Housing and Services, Living Environment Deprivation, and Crime.
[c]Major group occupational categories from UK Office for National Statistics SOC 2010: Group 1, Managers, directors & senior officials; Group 2, Professional occupations; Group 3, Associate professional & technical occupations; Group 4, Administrative & secretarial occupations; Group 5, Skilled trades occupations; Group 6, Caring, leisure & other service occupations; Group 7, Sales and customer service occupations; Group 8, Process, plant & machine operatives; Group 9, Elementary occupations.
[d]Related disability—total of 0–IIa for low and IIb–IV for high. Will not add up to 100% due to rounding or incomplete data.

Deprivation and Disability, Education Skills and Training Deprivation, Barriers to Housing and Services, Living Environment Deprivation, and Crime).

Total health care utilization cost and its constituent costs varied across the time points, as demonstrated in Table 2. There was a significant decrease in total health care cost over the 24 mo of the study, $F(4, 926) = 3.86$ ($P < 0.01$). Consultation costs remained significantly higher than both medication and appliance and treatment costs over time, $F(2, 2{,}064) = 109.36$ ($P < 0.0001$).

The 2 unbalanced regressions (Appendix Table 1; Table 2), controlled for age, sex, socioeconomic status, and origin and duration of pain, demonstrated that pain-related disability predicted utility (–0.08; 95% CI, –0.11 to –0.05; $P < 0.0001$) and costs (£221; 95% CI, 87–355; $P < 0.01$) over the 24-mo period. The predicted values from the regression models for the cost and utilities associated with the high and low pain-related disability states in the Markov model (Fig. 1) are shown alongside all other parameters for the Markov model in Table 3. The complete data on transitions between pain-related disability states are available in Appendix Table 4. The model (Fig. 1) estimated that the average cost of care per patient over their lifetime from age 25 y was £27,317 (95% CI, 26,558–28,046), and the average lifetime QALYs over that time were 17.54 (95% CI, 17.38–17.71).

Discussion

Consultation costs were identified over a 24-mo period as the major driver of health care utilization costs for those using NHS services for POFP. The dichotomized GCPS was predictive of health care utilization costs (as a proxy for health care need) and also individuals' health status as determined by the utility values from EQ-5D-5L. Moving from the low dichotomized GCPS state to the high state resulted in an additional £221 (95% CI, 87–355) health care utilization costs over a 6-mo period. The Markov model demonstrated that over the lifetime of a patient from age 25 y, a total expenditure of £27,317 (95% CI, 26,558–28,046) would result in 17.5 (95% CI, 17.3–17.7) y of perfect health (i.e., 17.5 QALYs). The data from this study also suggest that the current care pathway does not reverse high pain-related disability states to low states very frequently; there is a 65% probability of

Table 2.
Mean Cost of Health Care Utilization over the Duration of the Study.

Cost category		Cost at Time Period/£[a]				
		M0 (*n* = 198)	M6 (*n* = 172)	M12 (*n* = 155)	M18 (*n* = 136)	M24 (*n* = 129)
Mean consultation costs	Costs for specific areas					
	Primary medical care	214	150	143	126	124
	Primary dental care	25	19	15	17	17
	Physiotherapy	44	45	23	20	42
	Secondary specialist care	355	266	195	183	315
	Total	595	435	353	325	455
Mean medication costs by class of drug		0	0	0	0	0
	Simple analgesia (paracetamol, NSAIDs)	2	2	3	2	3
	Opioids	2	2	3	12	11
	Antidepressants (TCAs, SSRIs, SNRIs)	10	7	9	7	7
	Antiepileptics	23	46	49	66	63
	Migraine abortives and prophylactics (excluding antiepileptics)	3	3	2	4	2
	Topical therapy	0	1	1	1	0
	Anxiolytics	0	0	0	0	0
	Total	42	62	69	94	87
Mean appliance and intervention costs		0	0	0	0	0
	Primary dental care	71	55	52	54	39
	Secondary specialist care	2	1	1	82	1
	Total	73	56	53	135	39
Overall total mean cost (bootstrapped confidence interval[b])		710[c] (580–838)	554 (422–684)	474 (362–586)	554 (351–668)	582 (292–873)

Mx, month of data collection; NSAID, nonsteroidal anti-inflammatory drug; SNRI, Serotonin and Noradrenaline Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitors; TCA, Tricyclic antidepressants.
[a]Currency is pounds sterling at 2020 prices but can be converted to other national currencies using the validated Campbell and Cochrane Economics Methods Group (CCEMG) and Evidence for Policy and Practice Information and Coordinating Centre's (EPPI-centre) Cost Converter (Shemilt et al. 2010), available at http://eppi.ioe.ac.uk/costconversion/ (last accessed March 16, 2021).
[b]Bootstrapped confidence intervals of the total cost using a bias-corrected accelerated technique and 1,000 repetitions.
[c]One-way unbalanced analysis of variance demonstrated all time points had significantly less health care costs than M0, $F(4, 926) = 3.86$ ($P < 0.01$).

remaining in the high pain state for a 6-mo period once in that state.

This is the first attempt to model health care costs and benefits in POFP. As such, it provides an indication of the costs and benefits of the current care pathway(s). It corroborates other qualitative data in the POFP literature on the complexity of the care pathway resulting in multiple referrals and visits to health care professionals (Peters et al. 2015; Breckons et al. 2017). The study does, however, have limitations, including the risk of selection bias over time given the dropout rate and female predominance within the recruited sample, although attrition appeared relatively random and therefore it may be that there is imprecision in estimates as opposed to bias, and females more frequently present for care than males; the risk of

Table 3.
Parameters Used for the Markov Model.

Parameter	Value	Standard Error (95% CI)	Source	Assigned Distribution
Utility values				
Low pain-related disability	0.7284	0.0042 (0.7200–0.7370)	Unbalanced GLS regression random-effects model predicted values based on whole cohort's data.	Beta
High pain-related disability	0.6269	0.0063 (0.6156–0.6406)		
Cost				
Low pain-related disability	425	8.5 (408–442)	Unbalanced GEE regression model (identify link function, gamma family) predicted values based on whole cohort's data.	Gamma
High pain-related disability	674	13.2 (648–700)		

CI, confidence interval; GEE, generalized estimating equation; GLS, generalized least squares.

recall bias as participants were required to recall over a 6-mo period for each data collection point; the model's assumptions of sex, constant annual costs, QALY weights, and transition probabilities (except for risk of death); and under- or overestimation of unit costs in comparison to local costs throughout the United Kingdom. In the case of the latter, extensive sensitivity analyses were conducted and the results did not differ. The model's main limitation is its simplicity, but this is also merited given the lack of specificity of treatments available for POFP and the lack of any previous research in the health economics of POFP. The model, therefore, provides a best estimation of the situation currently and a baseline to facilitate future comparisons while accepting the model's limitations. The simplicity of the model does not allow for the idiosyncrasies of each POFP condition or indeed of each individual patient's illness trajectory to be modeled. The health states modeled lack some granularity that can mask clinically important differences. For example, within the "low" state, it was possible to slightly worsen in pain-related disability (Appendix Table 3) but still remain in the low state. Equally, as Table 2 demonstrates, there may be some trends within the data collected, although evidence is in support of these is very limited. For example, there may be a slight increase expenditure on opioids between M18 and M24, which is concerning as opioids have not demonstrated any great efficacy in the management of POFP. One further example of masking/artifact is in specialist care costs, which rose to £82 across the cohort at M18 but had been ≤£2 in preceding and subsequent months. This increase in cost at M18 was cross-checked and was a result of a patient having an intraoral biopsy and another patient undergoing a neurosurgical microvascular decompression that skewed the mean cost.

Despite the limitations of the model's definition of high and low state, it is clear that within the current care pathway, low states of pain-related disability are easier to maintain (87% probability) than high states are to reverse (35% probability) over a 6-mo period. This would fit with other research in the field (Von Korff and Dunn 2008) but may not be the full story as the model does not capture the time period over which patients may search for diagnosis and/or management, and the effects of this search account for the clustering that could occur in the transition probabilities from the study as people can transition more than once. It is apparent from qualitative data in the field (Peters et al. 2015; Breckons et al. 2017) that the search for diagnosis and management exerts a large impact on the individual. Due to the pathophysiology of persistent pain and dependent on the genotypic and/or phenotypic vulnerability of the individual, the time this search can take, and perhaps the search itself, could also potentially worsen outcomes, thereby affecting the probabilities of changing state.

It is crucial, therefore, that health care systems look to optimize the chances of staying in the low-severity state when presenting with POFP for the first time. Equally as important are expeditious diagnosis and management for both pain states due to the evidence suggesting early management is both most effective and cost-effective (Gatchel et al. 2006; Stowell et al. 2007). The challenge remains how best to do this within current health service structures. There are some data from the medical field on the clinical benefits and cost savings a hub-and-spoke model of care can provide in stroke with district-level hyperacute specialist centers feeding into local specialist hospital units after 72 h and then into community rehabilitation

following this (Fulop et al. 2019). Making or trialing this type of major system change ("large system transformation") clearly requires evidence (Best et al. 2012; Imison et al. 2014). In dentistry, to our knowledge, the only evidence that exists for hub-and-spoke care are data suggesting there are cost savings to be made with hub-and-spoke networks in rural areas for routine dental care whereby dentists flew out from major urban areas to provide care in local spokes (Dyson et al. 2012). This said, however, stratified care for persistent pain within a primary care context is known to be effective and cost-effective (Hill et al. 2011), and this could be provided in a single set of spokes (primary care feeding directly into specialist care at a secondary care hospital-based hub) or 2 spokes (primary care feeding into secondary hospital-based care, both of which are linked to tertiary subspecialist care at a hospital-based hub). There is therefore a need to trial a stratified hub-and-spoke approach to providing health care for POFP as it may help expedite diagnosis and appropriate management, thereby improving outcomes.

Conclusion

Given the prevalence of POFP, the lifetime costs of care are of considerable importance to the health service. A cohort of POFP patients would only accrue 17.54 QALYs per person through the care provided for POFP at a cost of £27,317 from age 25 y to the end of their lives. These data demonstrate the burden of POFP on health. They provide a foundation model for a "base case scenario" that can be used to perform economic evaluations of different ways care could be provided, for example, stratifying care in a hub-and-spoke model.

Author Contributions

J. Durham, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; M. Breckons, contributed to data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; L. Vale, contributed to conception, design, data analysis, and interpretation, drafted and critically revised the manuscript; J. Shen, contributed to data analysis and interpretation, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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