Economic evaluation alongside a randomised controlled trial to assess the effectiveness and cost-effectiveness of acupuncture in the management of chemotherapy-induced peripheral neuropathy

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Abstract:

Objective: to assess the cost-effectiveness of acupuncture in the management of chemotherapy-induced peripheral neuropathy in Hong Kong.

Methods: A within trial cost-utility analysis with the primary endpoint for the economic evaluation being the Quality Adjusted Life Year (QALY) and associated Incremental Cost Effectiveness Ratio (ICER) over 14 weeks of treatment. A secondary cost-effectiveness analysis was undertaken with the endpoint being change in pain as measured on the Brief Pain Inventory (BPI).

Results: Eighty-seven patients were randomised to acupuncture or usual care. Acupuncture resulted in significant improvements in pain intensity (8 & 14 week mean changes compared to usual care of -1.8 & -1.8, respectively), pain interference (8 & 14 week mean changes compared to usual care of -1.5 & -0.9, respectively) and indicators of quality of life and neurotoxicity-related symptoms. However, in the economic evaluation there was little difference in QALYs between the two arms (mean change 0.209 and 0.200 in the acupuncture and usual care arm respectively). Also, costs yielded deterministic ICERs of HK$616,965.62, HK$824,083.44 and HK$540,727.56 per QALY gained from the health care provider perspective, the societal perspective and the patient perspective, respectively. These costs are significantly higher than the cost-effectiveness threshold of HK$180,450 that was used for the base case analysis.

Conclusion: While acupuncture can improve symptoms and quality of life indicators related to CIPN, it is unlikely to be a cost-effective treatment for CIPN-related pain in health care systems with limited resources.

Key words: acupuncture, cost-effectiveness, peripheral neuropathy; chemotherapy

ClinicalTrials.gov Identifier: **NCT02553863**

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Introduction

Acupuncture as an intervention to manage a broad range of conditions has shown promising and positive results over the years, from managing low back pain[1], to functional dyspepsia[2], migraine[3], nausea/vomiting[4] and others, although negative and inconclusive evidence does exist for other conditions[4]. Economic evaluations increasingly underpin decisions in health care about allocation of resources and as such they should be incorporated in all trials of new interventions. However, the cost-effectiveness of acupuncture has received little attention in the literature, with a small body of evaluations showing that at times it can be cost-effective and at times it is not. Systematic reviews support the cost-effectiveness of acupuncture for chronic pain[5], dysmenorrhoea, allergic rhinitis, in osteoarthritis or headache[6]. On the other hand, several studies showed that acupuncture was not cost-effective, including in the management of irritable bowel syndrome[7], chronic low back pain (unless comorbid depression was included)[8] or allergic rhinitis[9].

Chemotherapy- induced peripheral neuropathy (CIPN) is a derangement in structure and function of peripheral motor, sensory and autonomic neurons, causing peripheral neuropathic signs and symptoms[10]. The prevalence of CIPN is reported to be 10-20% in patients during treatment and it may be as high as 100%, depending on the chemotherapy drug, dose-intensity, cumulative dose and other as yet unidentified risk factors[11,12]. CIPN has significant implications for patients' quality of life[13] alongside an impact on health care resource use, with those experiencing CIPN having more often outpatient visits and medication use, estimated to be at US$17,000 more in patients with CIPN than non-CIPN cancer patients[14].The management of CIPN is difficult with a limited number of treatment options available. There are some small-scale studies providing some initial evidence of effect, particularly in decreasing neuropathic pain, reviewed by Franconi[15]. We have recently completed the first fully-powered randomised trial in the management of chemotherapy-induced peripheral neuropathy[16]. Within this trial, we also assessed the cost-effectiveness of the use of acupuncture alongside usual care, versus usual care only, to allow for more informed health care decisions to be made in the future. Our trial included 87 patients randomised to acupuncture or usual care for 8 weeks[16]. The primary outcome for the trial was pain intensity or pain interference over the past week and secondary outcomes included patient-reported outcome measures with assessments taking place at baseline, end of treatment and week 14 from the beginning of treatment. At the end of the intervention, there were significant improvements in the acupuncture arm both in terms of primary and secondary outcomes. At 14 weeks there were still significant improvements in pain interference, neurotoxicity-related symptoms and functional aspects of quality of life ($p<0.05$) and at 20 weeks improvements sustained with regards to physical and functional well-being ($p<0.05$). In this article, we examined the cost-effectiveness of acupuncture in the management of CIPN with respect to cost per quality-adjusted life years (QALYs) and cost per unit reduction in pain intensity and pain interference, compared to usual care, over 14 weeks from randomisation.

Methods

The parent trial was an assessor-blinded randomised controlled trial of acupuncture for 8 weeks compared to a waitlist control arm receiving standard care, the latter group receiving acupuncture at the end of the trial. Adult patients having received neurotoxic chemotherapy and reporting numbness/tingling in the hands/feet and having signs of neuropathy according to their medical practitioner, were eligible to participate. Primary outcome was 'worst pain' using the Brief Pain Inventory (BPI)[17]. Other outcomes include the BPI pain interference item and the Functional Assessment of Cancer Therapy (FACT/GOG-Ntx)[18].

Measurement and valuation of outcomes

To determine the intervention's cost-effectiveness, we assessed the impact of the intervention on quality of life and reduction in pain over 14 weeks.

Quality of life was measured using the 27 item general assessment of quality of life sub-scale (FACT-G) of the Functional Assessment of Cancer Therapy (FACT/GOG-Ntx)[18]. The FACT-G questionnaire was completed by patients at home at baseline, at the end of the 8 weeks treatment and at 14 weeks post randomisation. Patient responses to the FACT-G questionnaire were converted to utility values using a mapping algorithm to convert to the EQ-5D scale and utility values relevant to the Chinese population[19]. The equation used was the following:

EQ-5D utility index = 0.238 + (0.014 x GP) + (0.006 X GE) + (0.008 X GF)

Where, GP is physical, GE is emotional and GF is functional well-being.

The utility values represent patients' quality of life and were multiplied by duration (t) in each health state to generate quality adjusted life years (QALYs)[20]. An area under the curve (AUC) approach was adopted for estimating QALYs with a linear transition assumed between adjacent time points.

$$QALY = \left(\left(\frac{Utility_{Baseline} + Utility_8}{2}\right) * t\right) + \left(\left(\frac{Utility_8 + Utility_{14}}{2}\right) * t\right)$$

Where, $Utility_{Baseline}$, $Utility_8$ and $Utility_{14}$ are the utility scores at baseline, week 8 and week 14, respectively.

The secondary outcome measure was reduction in pain as measured by the 'worst pain during the past week' measured on the Brief Pain Inventory (BPI), completed by patients at each time point. Reduction in pain was calculated at 8 and 14 weeks (with respect to baseline) on the two dimensions of the BPI questionnaire: pain severity and pain interference. The Pain Severity subscale is calculated as the mean of four pain items, from question 3 to 6; and the Pain interference subscale is calculated as the mean of the seven interference items, from question 9a to 9g.

Measurement and valuation of resource use

Costs related to the intervention and wider healthcare utilisation

Healthcare resource use was estimated from the perspective of the healthcare provider and was collected for the trial period of 14 weeks from randomisation. This included primary care such as GP, nurse visits and home visits as well as secondary care such as outpatient visits and other hospital admissions. Additionally resource use and cost data from a patient perspective were obtained to enable analyses from patient and societal perspectives. The healthcare provider perspective included the costs to provide medical treatments. The patient perspective included costs for healthcare treatment and services, medications (paid for by patient), travel costs, food and drink costs and other expenses related to treatment that were paid for out of pocket. The societal perspective included all costs for healthcare, patient perspective costs and also costs associated with productivity loss from time out of work due to illness.

Resource use was captured using a bespoke questionnaire which patients completed at 14 weeks post randomisation. To determine the costs associated with the intervention and wider healthcare utilisation, unit costs were assigned to healthcare resource use using charge values from the Hospital Authority of Hong Kong[21], and price year 2017. Charges are made up of two parts, part paid by the patient and part paid by the insurer. The sum of these two charges was used as the total cost of the relevant healthcare service. Costs were assigned on a per unit basis, with unit values taken from the resource use data collected within the trial. All recorded use of healthcare services that occurred within the trial period were costed irrespective of whether their use was directly associated with the treatment of cancer or the associated neuropathy. Unit costs for the main resource use items are presented in Table 1. Patient's use of healthcare resources and total costs were calculated for the intention-to-treat (ITT) population.

Cost-effectiveness analysis

Primary analysis

The primary analysis was a cost-utility analysis in which an incremental cost per QALY gained, due to acupuncture compared to usual care, was calculated over 14 weeks. As the intervention is intended to limit the side-effects of the chemotherapy, the benefits are not expected to continue after treatment has ceased and consequently this short time-horizon is appropriate for the research question being explored. For the main analysis, a healthcare provider perspective was adopted; a patient perspective and a societal perspective were also adopted for subsequent analyses. As the timeframe of the trial was less than a year, discounting of the costs and benefits was not required.

The incremental cost per QALY gained as a result of the use of acupuncture compared to usual care was calculated by dividing the mean difference in cost of the two trial arms by the mean difference in QALYs to produce an incremental cost-effectiveness ratio, as follows:

$$ICER = (Cost_A - Cost_B)/(QALY_A - QALY_B)$$

The ICER represents the additional cost per QALY gained for the intervention compared to the best alternative (in this case usual care) [22].

After considering that, first, a single ICER threshold value for decision making is not officially available in Hong Kong and, second, the gross domestic product per capita threshold is no longer recommended by World Health Organisation[23], the cost-effectiveness threshold was set at $23,105 based on a research paper by Woods et al.[24] on country-level cost-effectiveness thresholds. The paper indicates a threshold range for Hong Kong of $17,409 - $28,801; hence the midpoint was selected as the reference threshold. This threshold range was converted to Hong Kong dollars using an exchange rate of 1 US dollar=7.81 Hong Kong dollars to give HK$135,964 - HK$224,936. The mid-point of HK$180,450 was used as the cost-effectiveness threshold for the base case analysis. (In line with current best practice for economic evaluation, we did not adjust the cost-effectiveness threshold with respect to inflation (Drummond et al, 2015; Claxton et al, 2015)). Alternative thresholds were explored in the uncertainty analysis.

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Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L. and Torrance, G.W. 2015. *Methods for the economic evaluation of health care programmes.* Oxford university press.

Claxton, K, Martin, S, Soares, M, Rice, N, Spackman, E, Hinde, S, Devlin, N, Smith, PC & Sculpher, M 2015, 'Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold', Health technology assessment, vol. 19, no. 14, pp. 1-542. https://doi.org/10.3310/hta19140

Secondary analysis

In the secondary cost-effectiveness analysis, the incremental cost was compared to the change in BPI scores, in the two pain subscales, between baseline and 8 weeks as well as baseline and 14 weeks, as a result of the use of acupuncture compared to usual care.

Missing Data

Where patients indicated they had used a particular health care service but had not recorded the number of times it had been used, the mean of visits to that health service was imputed. For the BPI, only 25 patients responded "YES" to the first question ("Throughout our lives, most of us have had pain from time to time. Have you had pain other than these everyday kinds of pain today?") and were prompted to answer the remaining items. Hence, in the original dataset, only these 25 subjects had a BPI score while the others showed missing values. It was agreed that those who responded "No" in the first question should have a BPI score of '0', so the missing values were imputed with zeros.

Multiple imputation was employed to account for missing EQ-5D data. This approach is recommended for economic analyses conducted alongside clinical trials as it reflects the uncertainty inherent in replacing missing data[25]. The imputation was performed in Stata Version 14 using predictive mean matching to perform multiple imputation by chained equations. Predictive mean matching was used due to the non-normal distribution of EQ-5D scores. This technique ensures that only plausible values of the missing variable are imputed as the imputed value is drawn from another individual whose predicted value is close to the predicted value of the individual with the missing observation[26].

Sensitivity Analyses

Alternate scenarios were explored in the sensitivity analyses to test the robustness of the main trial analysis results. The effect of not imputing missing quality of life data was explored with an analysis including only complete cases. Additionally, sensitivity analyses were performed to explore the uncertainty around the costs by adding and subtracting 20% of the costs and outcomes and assessing the subsequent impact on the ICERs. The value of 20% is essentially arbitrary but was considered likely to represent any uncertainty that might exist in the values. The increase and decrease in costs by 20% was explored both from the health care provider perspective and the societal perspective.

Further sensitivity analyses were conducted to explore the effect of assumptions made in the base case analysis related to patient perspective costs. In the base case analysis, it was assumed that the costs reported for prescription medications were related only to the trial period, not for the whole time the medication was taken. The effect of this was explored in a sensitivity analysis in which it was assumed that the reported cost was for the whole time the medication was taken and the relevant cost for the trial period was calculated as the total cost divided by the number of days taken to estimate a cost per day which was multiplied by 98 (98 days equal to 14 weeks – the length of the trial). In the base case analysis it was also assumed that the treatment cost was paid by the patient out-of-pocket. The effect of this was explored in a sensitivity analysis in which it was assumed that the treatment was paid for by an insurer/ public provider instead of by the patient.

Additional sensitivity analysis was also performed to explore the robustness of the secondary analysis results. The secondary analysis was based on changes in BPI (the primary outcome of the main trial analysis). As only a small number of patients had the primary outcome, the effect of acupuncture on other neurotoxic symptoms was also explored in a sensitivity analysis which instead used the outcome of neurotoxicity from the subscale of FACT/GOG.

Uncertainty Analysis

The level of sampling uncertainty around the ICER was determined using a non-parametric bootstrap to generate 10,000 estimates of incremental costs and benefits. The bootstrapped estimates were plotted on the cost-effectiveness plane to illustrate the uncertainty surrounding the cost-effectiveness estimates[27]. Net monetary benefit was calculated for each of the bootstrapped estimates as:

$$NMB = (\lambda \times QALYs) - costs$$

Where, λ is the value a decision maker would be willing to pay per incremental QALY gained, i.e. the cost-effectiveness threshold.

The expected net monetary benefit was used to estimate the probability that acupuncture is cost-effective given a range of threshold values (λ=£0 to λ =£100,000) which is plotted on the cost-effectiveness acceptability curve (CEAC)[28]. The cost-effectiveness frontier (CEF) was also plotted to show the intervention that provides the highest net benefit for a given threshold.

Ethical approval

Ethical approval was granted by the Human Research Ethics Review Committee of the Hong Kong Polytechnic University (HSEARS20141011004; approved 29 October 2014) and the study hospital (CREC Ref. 2014.529-T; approved 18 November 2014) All participants signed a consent form. The trial was prospectively registered with ClinicalTrials.gov, identifier: NCT02553863.

Results

Sample

The first patient was recruited in November 2015, recruitment was completed in March 2017 and last patient follow-up was completed in May 2017. Among the 87 participants, the acupuncture arm had a higher share of male patients (62.5%), while in the usual care arm there was a higher share of female patients (55.6%). The mean age was 56.3 (SD=7.35) years old in the acupuncture arm and 58 (SD=7.98) in the usual care arm.

Resource use and costs

Resource use and costs incurred by patients in each arm are presented in Table 2. Average total healthcare costs were HK$8,849 and HK$3,286, for the acupuncture and usual care arms of the trial, respectively, meaning that patients receiving the intervention, on average, showed higher total cost associated with the use of health care services (primarily due to the acupuncture costs). Also, based on the control arm costs above (over 14 weeks), if costs remain constant, patients with CIPN cost the healthcare system HK$12,205 (US$1,565) annually.

Outcomes

Mean QALYs gained from baseline to 14 weeks were 0.209 and 0.200 for acupuncture and usual care, respectively (presented in Table 3). In the usual care arm, the change from baseline regarding pain severity increased 0.5 points from baseline to 8 weeks and increased1 point from baseline to 14 weeks, while for the acupuncture arm these –decreased by 1.3 points and 0.8, respectively. Pain interference increased 0.5 points from baseline to week 8 and increased 0.8 points from baseline to week 14, whereas in the acupuncture group pain interference decreased by 1 and 0.1 points, respectively. Mean BPI scores are presented in Supplementary Table 1.

Cost-effectiveness analysis

Primary analysis

The cost-effectiveness results estimated from the healthcare provider perspective, the societal perspective and the patient perspective are each presented in Table 1. The QALYs and costs yielded deterministic ICERs of HK$616,965.62, HK$824,083.44 and HK$540,727.56 per QALY for the health care provider perspective, the societal perspective and the patient perspective, respectively.

The healthcare provider perspective was taken as the base case analysis which was used to perform uncertainty analysis around the cost-effectiveness estimates. Bootstrapped uncertainty analysis produced a cloud of points which is predominantly in the north-east quadrant and entirely above the threshold, with a mean simulation ICER of HK$598,289.19 (Figure 1). The CEAC in Figure 2 suggests that acupuncture had 6% probability of being cost-effective at the HK$180,450 threshold.

INSERT TABLE 1 & FIGURE 1 & FIGURE 2 HERE

Secondary Analysis

Regarding BPI change over time compared to baseline, the cost-effectiveness results estimated for the two subscales (pain severity and pain interference) and over two time periods (8 and 14 weeks) are shown in Table 2. The assumption was made that the costs incurred are evenly spread across the trial period; therefore a proportion was used for the cost-effectiveness analysis over 8 weeks. The results show that acupuncture is most cost-effective in reducing pain severity from baseline to 8 weeks.

INSERT TABLE 2 HERE

Sensitivity analysis

The cost-effectiveness results for each scenario explored in the sensitivity analyses are presented in Table 3. In each case the results of the sensitivity analysis, for both the healthcare provider perspective and the societal perspective, support the results of the base case analysis and indicate that, compared to a cost-effectiveness threshold value of HK$180,450, acupuncture alongside usual care for the management of chemotherapy-induced peripheral neuropathy is not a cost-effective use of health care resources.

For patient perspective costs, alternative assumptions around the costs of prescription medication had little impact on the ICER estimates. However, the cost of acupuncture appears to be a key driver of the difference in patient costs between the control and intervention arms of the trial. When it is assumed that treatment (acupuncture) is paid for by an insurer or public provider, there is no significant difference in patient out of pocket costs between the 2 arms (p=0.87).

Sensitivity analysis exploring the impact of considering other neurotoxic symptoms is also shown in Table 3. As in the analysis of BPI, estimates of cost-effectiveness are presented for the periods: baseline to 14 weeks, and baseline to 8 weeks. Costs incurred were assumed to be evenly spread across the trial period and therefore a proportion of the 14 week costs were used for the cost-effectiveness analysis over 8 weeks. The results confirm the robustness of the secondary analysis with BPI mean score showing that acupuncture is most cost-effective in reducing symptoms of neurotoxicity from baseline to 8 weeks.

INSERT TABLE 3 HERE

Discussion

This is the first health economic analysis of acupuncture for managing CIPN. While the trial showed acupuncture to be an effective treatment of CIPN in relation to pain and other neuropathic symptoms and quality of life indicators, the results of the economic evaluation indicated that the probability of acupuncture being cost-effective is 6%. The cost of acupuncture appears to be a key driver of the difference in patient costs between the control and intervention arms of the trial, a finding of other studies where acupuncture was effective but not necessarily cost-effective [9]. On the other hand, there was little difference in QALYs gained between the two arms despite benefits in terms of pain reduction. On this point, it is worth considering that the EQ-5D is a generic measure of quality of life and may not be sensitive enough to pick up these changes in quality of life. Also QALYs were estimated using a mapped algorithm for EQ-5D. Although this was validated for the Chinese/Hong Kong population, this could be a source of bias. The sensitivity analyses conducted supported the results of the base case analysis and indicate that, compared to a cost-effectiveness threshold value of HK$180,450, acupuncture alongside usual care for the management of CIPN is not a cost-effective use of resources. However, pain in this sample was mild (mean=1.2; 2.1, sd=0.3; 0.4 in the control and intervention groups respectively) and this may be a reason for the small clinical changes observed, reflected in a non-cost effective outcome in this evaluation. The low levels of pain experienced by patients recruited in this study poses a limitation to the analysis as consequently healthcare resource use may have been lower than in other similar patient groups.

The results of the secondary cost-effectiveness analysis suggested that acupuncture reduces pain severity and pain interference over both 8 and 14 weeks but that it is most cost-effective in reducing pain severity from baseline to 8 weeks. As the key issue is the actual acupuncture cost, it indicates that for patients with health insurance that will cover the cost of the treatment, the patient can obtain the benefits of the treatment with little additional out-of-pocket costs. However, this may raise an equity issue for those patients who do not have appropriate health insurance as their out-of-pocket costs to obtain this treatment may be much higher. Access to acupuncture treatment may also be an issue, particularly in rural areas, as patients may be willing to pay for such an effective service but there is unavailability of acupuncture delivery. In addition, given that the cost of acupuncture is a key diver of the difference in cost between groups, and that the cost of acupuncture varies in different countries, the cost-effectiveness of acupuncture for CIPN will vary in different countries and contexts.

It is important to note that the treatment comparator used in an acupuncture trial can be fundamental as to whether the acupuncture will be cost-effective or not. In our case, the treatment comparator was usual care, which in reality involved very little supportive care and primarily painkillers if there was any pain or vitamin B. If the comparator was another treatment, the results may have been different. Also, more wide use of acupuncture in a clinical setting may decrease the costs of treating CIPN patients. Furthermore, this economic conclusion is tentative as we have not assessed long-term costs beyond 14 weeks, and if symptoms have not reverted to baseline beyond the 14-week assessment it is possible that functioning may have improved and cost-effectiveness may become more likely.

Lastly, an important consideration is that cost-effectiveness is determined by the cost-effectiveness threshold and there is no pre-defined cost-effectiveness threshold for Hong Kong. We used the threshold from Woods et al [23] as it provides a plausible estimate of health opportunity cost in Hong Kong. However note that further research would be of use to estimate appropriate cost-effectiveness thresholds for Hong Kong given the unique healthcare landscape and accounting for decision making from different perspectives (e.g. healthcare provider, department of health, insurer etc)[29]. The choice of threshold will impact the results and it may be helpful for decision makers to use the CEAC to explore potential cost-effectiveness for cost-effectiveness thresholds relevant to their specific decision making context.

Conclusion

The economic evaluation indicated that acupuncture alongside usual care for the management of chemotherapy-induced peripheral neuropathy, while effective for managing pain and other neuropathic symptoms and improving quality of life, is unlikely to be a cost-effective use of healthcare resources when compared with a cost-effectiveness threshold based on opportunity costs elsewhere in the system.

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Conflict of Interest:

Authors declare no conflict of interest.

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Table 1 Unit costs of health care services

Resource item	Patient charge (HKD)	Insurance charge (HKD)	Source	Details
GP surgery visit	$50	$445	Hospital Authority	General clinic
GP home visit	$80	$445	Hospital Authority	General clinic
District nurse surgery visit	$80	$535	Hospital Authority	Community nursing service
District nurse home visit	$80	$535	Hospital Authority	Community nursing service
Oncology specialist visit	$135 first visit, $80 subsequent visits	$1190	Hospital Authority	Specialist clinic
Hospital oncology clinic	$96	$895	Hospital Authority	Clinical oncology clinic
Psychologist	$60	$1730	Hospital Authority	Psychiatric day hospital
Physiotherapist	$55	$1730	Hospital Authority	Rehabilitation day hospital
Occupational health visit	$55	$1730	Hospital Authority	Rehabilitation day hospital
Dermatologist	$135 first visit, $80 subsequent visits	$1190	Hospital Authority	Specialist clinic
Traditional Chinese medicine practitioner	$50	$445	Hospital Authority	General clinic
Other hospital departments: internal medication, blood taking	$19	$100	Hospital Authority	Hospital attendance for injection or dressing
Notes: 1, Data was collected on contacts with healthcare services by telephone or email (reported below) but no costs are included in the analysis for these services as they are not charged for.				

Table 2 Resource use and costs

Healthcare	**Resource use *Mean (SD)***		**Patient cost *Mean (SD)***		**Hospital cost *Mean (SD)***	
	Usual care	**Acupuncture**	**Usual care**	**Acupuncture**	**Usual care**	**Acupuncture**
GP	0.49 (0.86)	0.98 (1.92)	24.42 (0.86)	48.86 (96.14)	217.33 (0)	434.89 (855.64)
GP (home)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
District nurse	0 (0)	0 (0)	0 (0)	0 (0)	0 (1.37)	0 (0)
District nurse (home)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oncology hotline[1]	0 (0)	0.14 (0.51)	0 (0)	0 (0)	0 (0)	0 (0)
Oncology specialist	0.12 (0.39)	0.5 (1.21)	14.42 (0)	52.5 (115.76)	138.37 (4.05)	595 (1440.4)

Oncology specialist (home)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hospital oncology unit	1.51 (3.59)	1.5 (4.28)	145.12 (0.39)	144 (410.7)	1352.91 (0.15)	1342.5 (3828.92)
Psychologist/Psychiatrist	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychologist/Psychiatrist (home)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Physiotherapist	0.21 (1.37)	0.32 (1.07)	11.51 (0)	17.5 (59.04)	362.09 (42.78)	550.45 (1857.01)
Physiotherapist (home)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	2.02 (4.05)	2.56 (6.25)	98.84 (3.59)	102.98 (208.9)	98.84 (0)	102.98 (208.9)
Treatment (acupuncture)[2]	-	-	0 (0)	4697.73 (589.24)	-	-
Prescription medication[3]	-	-	1028.74 (0)	1194.32 (3132.55)	-	-
Non-prescription medication[3]	-	-	789.35 (46.79)	959.82 (2794.78)	-	-
Travel[4]	-	-	471.4 (345.1)	401 (518.84)	-	-
Food and drink[5]	-	-	1631.98 (75.49)	952.5 (1236.83)	-	-
Other expenses[5]	-	-	3702.14 (203.39)	4223.64 (15236.42)	-	-
Productivity loss (days)[6]	50 (0)	55.11 (45.65)	15852.27 (380.73)	17789.77 (24003.07)	-	-

Notes:
[1] Oncology hotline is a free service;
[2] The treatment cost is assumed to fall to patients if implemented in practice (outside of trial setting);
[3] These were reported as patient costs, no itemised prescription data was available;
[4] The sum of out of pocket costs for taxis, public transport, fuel, additional miles and parking;
[5] Cost data reported only;
[6] calculated using a human capital approach based on days out of work and associated income

Table 2 Cost-effectiveness analysis

Treatment group	**Cost (HKD$)** ***Mean (SD)***	**Incremental cost**	**QALYs** ***Mean (SD)***	**Incremental QALYs**	**ICER (HK$/ QALY)**
Health care provider perspective					
Usual care	$3,286.16 (6009.04)		0.200 (0.022)		
Acupuncture	$8,849.25 (6182.91)	$5,563.09	0.209 (0.021)	0.009	$616,965.62
Societal perspective					
Usual care	$12,384.40 (19230.74)		0.200 (0.022)		
Acupuncture	$19,815.03 (22955.75)	$7,430.63	0.209 (0.029)	0.009	$824,083.44
Patient perspective					
Usual care	$7,919.19 (17636.65)		0.200 (0.022)		
Acupuncture	$12,794.84 (17793.87)	$4,875.65	0.209 (0.029)	0.009	$540,727.56

Table 3 Cost-effectiveness in reducing pain

Treatment group	**Cost (HKD$)** ***Mean***	**Incremental cost**	***Mean change in BPI score from baseline***	**Incremental change in BPI**	**ICER (HK$/unit reduction BPI score)**
14w change Pain Severity					
Usual care	$3,286.16		1.0		
Acupuncture	$8,849.25	$5,563.09	-0.8	-1.8	$3,090.60
14w change Pain Interference					
Usual care	$3,286.16		0.8		
Acupuncture	$8,849.25	$5,563.09	-0.1	-0.9	$6,181.21
8w change Pain Severity					
Usual care	$1,877.80		0.5		
Acupuncture	$5,056.71	$3,178.91	-1.3	-1.8	$1,766.06
8w change Pain Interference					
Usual care	$1,877.80		0.5		
Acupuncture	$5,056.71	$3,178.91	-1	-1.5	$2,119.27

Table 4: Sensitivity analysis – cost-effectiveness results

Treatment Group	Cost ($HKD) *Mean (SD)*	Incremental cost	QALY *Mean (SD)*	Incremental QALY	ICER (HK$/QALY)
Health care provider perspective: Complete case analysis					
Usual care n=39	3597.82 (6230.45)		0.1997 (0.03)		
Acupuncture n=42	9134.93 (6169.93)	5537.11	0.2087 (0.022)	0.0089	618,280.5
Health care provider perspective: 20% increase costs					
Usual care n=43	3943.40 (7210.85)		0.2003 (0.029)		
Acupuncture n=44	10619.1 (7419.49)	6675.70	0.2093 (0.022)	0.0090	740,359.50
Health care provider perspective: 20% decrease costs					
Usual care n=43	2628.93 (4807.24)		0.2003 (0.029)		
Acupuncture n=44	7079.40 (4946.33)	4450.47	0.2093 (0.022)	0.0090	493,573.03
Societal perspective: 20% increase in costs					
Usual care n=43	14861.28 (23076.89)		0.2003 (0.029)		
Acupuncture n=44	23778.03 (27546.9)	8916.75	0.2093 (0.022)	0.0090	988,899.94
Societal perspective: 20% decrease in costs					
Usual care n=43	9907.52 (15384.59)		0.2003 (0.029)		
Acupuncture n=44	15852.02 (18364.6)	5944.50	0.2093 (0.022)	0.0090	659,266.75
Patient perspective: Prescription medication cost for whole duration prescribed					
Usual care n=43	7909.76 (17626.42)		0.2003 (0.029)		
Acupuncture n=44	12718.82 (17820.43)	4809.05	0.2093 (0.022)	0.0090	533,341.81
Patient perspective: Treatment (acupuncture) paid for by insurer/ public provider					
Usual care n=43	7919.19 (17636.65)		0.2003 (0.029)		
Acupuncture n=44	8097.11 (17738.34)	177.93	0.2093 (0.022)	0.0090	19,732.82
14w change in FACT/GOG NtxS (from baseline)					
Usual care	$3,286.16		0.96		
Acupuncture	$8,849.25	$5,563.09	3.23	2.27	$2,446.73
8w change in FACT/GOG NtxS (from baseline)					
Usual care	$1,877.80		1.73		
Acupuncture	$5,056.71	$3,178.91	4.90	3.16	$1,005.98

Supplementary table 1: BPI mean scores

Variable	Usual care (n=43)	Acupuncture (n=44)
baseline		
Pain Severity	1.3	2.1
Pain interference	0.9	1.4
8 weeks		
Pain Severity	1.8	0.8
Pain interference	1.4	0.4
14 weeks		
Pain Severity	2.3	1.3
Pain interference	1.7	1.3