BMJ Open

Cost-utility analysis of a trial comparing an enhanced behaviour change intervention to physiotherapy in patients with chronic low back pain.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019928
Article Type:	Research
Date Submitted by the Author:	04-Oct-2017
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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Lower back pain, economic evaluation, QALYs, cost-utility analysis, cost-effectiveness analysis, physiotherapy

COST-UTILITY ANALYSIS OF A TRIAL COMPARING AN ENHANCED BEHAVIOUR CHANGE INTERVENTION TO PHYSIOTHERAPY IN PATIENTS WITH CHRONIC LOW BACK PAIN.

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Funding: The study was supported by Maccabi Healthcare Services (an Israeli Public Health organisation).

Key words: Lower back pain; economic evaluation; QALYs; cost-utility analysis; cost-effectiveness analysis; physiotherapy

Word count: 3423

ABSTRACT

Objectives: To assess the cost-effectiveness of an enhanced trans-theoretical model of behaviour change in conjunction with physiotherapy compared to standard care (physiotherapy).

Design: Cost-utility and cost-effectiveness analysis alongside a cluster controlled trial.

Setting: The trial was conducted was conducted in eight centres within the Sharon district, Israel.

Participants: 220 participants aged between 25 to 55 years who suffered CLBP for a minimum of three months were recruited. Informed consent was obtained for all participants.

Interventions: The intervention used a model of behaviour change that sought to increase the adherence and implementation of physical activity in conjunction with physiotherapy. The control arm received standard care in the form of physiotherapy.

Primary and secondary measures: the primary outcome was the incremental cost per quality adjusted life year (QALY) gained by the intervention arm compared to standard care. The secondary outcome was the incremental cost per Roland Morris Disability Questionnaire (RMDQ) point.

Results: The cost per QALY point estimate was 10,645NIS (£1737.11). There was an 88% chance the intervention was cost-effective at the 50,000NIS per QALY threshold. Excluding training costs, the intervention dominated the control arm resulting in fewer physiotherapy and physician visits whilst improving outcomes.

Conclusions: The ETMI intervention appears to be a very cost-effective intervention leading to improved outcomes for low cost. Given limitations within this study, there is justification for examining the intervention within a larger long term randomised controlled trial.

Trial registration number: NCT01631344

Word count: 3423

Strengths and limitations of this study:

- Novel intervention that integrates behaviour change theory into physical therapy appointments.
- Health care and medication data was collected via routine data sources providing detailed information on health and medication use.
- Generalisability to the region - recruitment methods reflected actual referral processes with nearly all referrals within the Sharon district being included in the study.
- Due to the recruitment method reflecting reality, selection bias cannot be ruled out.
- No Israel specific SF-6D algorithm exists and thus QALYs will differ if preferences differ between countries.

INTRODUCTION

Low back pain is the number one cause of daily disability worldwide [1]. It remains highly prevalent and difficult to treat [2]. Increased physical activity is recommended as the most promising and effective approach to treating patients with chronic lower back pain (CLBP) [3]. Evidence suggests that physical activity is effective in improving function, preventing further pain, and improving return to work outcomes [4,5]. However, adherence to advice to start, and maintain higher levels of physical activity is problematic [6,7] with many people failing to continue to exercise in the long term [7]. Criticisms of existing intervention suggest the need for theory driven interventions that focus on the key obstacles to long term rehabilitation [7]. An enhanced trans-theoretical model intervention (ETMI) of behaviour change was developed to address this [8]. ETMI seeks to increase the adherence and implementation of physical activity by harnessing theory–informed counselling, based on behaviour change principles to overcome barriers to exercise. ETMI matches practitioners counselling, about patient's choice of recreational physical activity to patient's readiness to change. Additionally, it aims to tackle fear of movement, whilst enhancing reassurance and education about CLBP.

In the primary clinical paper [8], ETMI was found, in an Israeli study, to be more effective than usual physiotherapy as assessed with the Roland-Morris Disability Questionnaire [9] as a primary outcome. In addition, it performed better on the physical scale of the SF-12 questionnaires [10], worst and average levels of pain, and self-report of levels of physical activity. As well as demonstrating effectiveness, it is important to consider cost-effectiveness of implementing new interventions. In Israel, interventions that have a cost per quality adjusted life year less than 50,000 New Israeli Shekels tend to be approved by the Public Committee and can therefore be considered cost-effective [11]. The equivalent value in the UK is £30,000 per quality adjusted life year [12]. Here we present the cost-effectiveness analysis of the ETMI intervention compared to usual care.

METHODS

The ETMI study was a multi-centred pragmatic controlled trial of patients with CLBP. It is described in detail elsewhere [8]. The trial ran between February 2011, and July 2012. Ethics approval was obtained from both the ethics committee of the Maccabi Healthcare Services (a public health

organisation), and Tel Aviv University. Informed consent was mandatory for inclusion within the trial. The trial was registered on clinicaltrials.gov (NCT01631344). This analysis uses a one year time horizon (reflecting the clinical paper), hence costs and outcomes were not discounted. Prices are presented in 2012 terms (the year the trial concluded). Costs are presented in New Israeli Shekels (NIS), with Great Britain Pounds (GBP) in parentheses. The exchange rate from mid-2012 is used to convert NIS to GBP (6.128NIS = £1).

Population

The trial focussed on people aged between 25 to 55 years with CLBP (as defined by a duration of over 3 months) who were referred to the Maccabi Health Services physical therapy clinics within the Sharon district. All participants were required to speak Hebrew fluently. Patients with the following contraindications were excluded: rheumatic diseases, tumours, fractures, fibromyalgia, previous spinal surgery, pregnancy, post-car (or work) accident pain.

Recruitment and arm allocation

Eight participating centres were recruited. Across the eight centres, 11 physiotherapists administered the intervention, whilst 23 provided normal care. All physios had in excess of four years of experience. All referrals for physiotherapy from general practice or orthopaedic secondary care within the district were allocated by an independent party to the nearest physiotherapist according to geographic location without knowledge of whether the physiotherapist was within the trial. Although not randomised, the allocation of participants was not under the influence of the study team. Upon arriving for treatment, eligibility was assessed and eligible participants were provided with information about the trial. Those who did not consent received treatment as usual.

Interventions

The two arms of the trial can be characterised as follows:

1. Usual care (control) – The usual care group received standard physical therapy treatment, this could include: mobilisation, manipulation, back exercises, postural training, attending back school, electrical stimulation, short wave diathermy, cooling, and stretching.

2. With the exception of back exercise, the intervention did not use any of the methods associated within the usual care arm. The main aim of the intervention was to facilitate participation in a chosen recreational physical activity through matching and supporting the patient's cognitive readiness to change, and so, reducing known barriers to physical activity such as low motivation, low self-efficacy, and fear of movement. A semi-standardized protocol was used for the intervention; a full exposition of the enhanced intervention can be found in Ben-Ami et al [8].

Resource use and costs

The costing perspective adopted for this study was a health care perspective, wider societal costs were not considered. The healthcare perspective included the cost of training staff to deliver the intervention, the cost of delivering the intervention (including the time and materials used) and healthcare costs. Information on health care use was captured primarily through the computerised medical records that are available through the Maccabi Healthcare Service. These records were used to extract information on physiotherapist appointments, general practitioner appointments and all pain and inflammation medication; this includes over the counter purchases. No data on hospitalisation was captured. Training costs were recorded by the trial team. Unit costs were obtained from the Ministry of Health [13,14]. Resource use was retrospectively collected for the three months prior to the start of the trial to assess baseline resource use, and for the twelve months of follow up. Consequently, information was available for: all physiotherapy appointments; all doctor appointments; all pain and inflammation medication; and the costs associated with setting up and delivering the intervention.

Outcomes

The primary health economic outcome was incremental cost per Quality Adjusted Life Years (QALYs). QALYs are a unit of outcome that combine both quantity and quality of life into a single metric. QALYs have been widely adopted in many countries around the world (e.g. the National Institute for Health and Care Excellence [12]). To obtain utility values for QALY calculation within this study, the SF-12 was included at baseline, and both follow ups (3 months and 12 months). The SF-12 is a generic health related quality of life questionnaire examining 12 domains of health [10]. Algorithms exist to convert SF-12 scores into SF-6D utility values [15]. As the version 1 (US) SF-12 instrument was used,

the appropriate algorithm provided by the University of Sheffield was used to calculate utility values. From baseline through the follow ups, these health utilities were combined with length of life information to calculate QALYs. QALYs were calculated using the trapezium rule which calculates the area under the curve [16]. The second outcome considered was the Roland-Morris Disability Questionnaire (RMDQ): a common and well validated back pain specific measure [9,17,18] suitable to this setting which formed the primary outcome in the main Ben-Ami et al study [8].

Statistical analysis

The economic analysis is characterised as a within-trial cost-utility analysis examining the incremental cost per QALY associated with introducing the intervention. First, costs and outcomes between the two arms were compared in isolation. They were then combined within a cost-effectiveness analysis which analysed both costs and outcomes simultaneously. Given the hierarchical structure of the data, appropriate statistical methods were required [19].

Analysis of costs and QALYs

We included relevant characteristics and baseline scores as co-variates within a regression framework to control for baseline differences in characteristic or health states [20–22]. Due to the clustered nature of the data, it was necessary to use analytic methods that accounted for clustering [19]. Multi-level models were adopted allowing for random effects at the physiotherapist and centre level. Finally, the skewness of the data can affect the method of analysis used. Given the skewed cost data collected in the trial, it was necessary to adopt a method that could handle non-parametric data. Generalized linear models [23] were therefore implemented using a gamma family, and identity link function which gave the best model fit for the data. Thus, the final model was a multi-level generalised linear model controlling for baseline characteristics (including age, gender, body mass index, health state and years of education). This simultaneously addressed the three specified issues relevant to the data. This was implemented within Stata [24] using the 'meglm' code.

Examining cost-effectiveness

An incremental cost-effectiveness ratio can be calculated by dividing the incremental costs by incremental QALYs. A simple cost per QALY approach however does not reflect that costs and outcomes may be correlated, and does not characterise the uncertainty that is present [22,25]. To address this, we used the net benefit approach which combines costs and QALYs into a single metric of net benefit [26]. The net-benefit approach multiplies QALYs with the willingness to pay (WTP) for those QALYs by the decision maker, and then subtracts costs [26]. This was done for a range of willingness to pay values. To control for clustering, a hierarchical approach was necessary [27]. A multi-level regression framework was therefore used for each WTP level to assess the cost-effectiveness whilst also controlling for baseline imbalances and clustering. Given the parametric nature of net-benefits, a generalised linear model was not required, hence the 'mixed' Stata command was used. Within the model, for any willingness to pay, if the intervention co-efficient (the incremental net benefit) was greater than zero, then the intervention was deemed cost-effective at that willingness to pay. Using data from the output of the net benefit regressions, cost-effectiveness acceptability curves (CEACs) were generated to characterise the uncertainty in decision making at each level of willingness to pay [21,26].

Sensitivity analyses

We ran three sensitivity analyses:

1. Cost per RMDQ point. The analysis methods outlined above were followed, however the outcome of interest was 'difference in RMDQ' score rather than QALYs.
2. Multiple imputation in Stata for missing data. A fixed effect approach for multiple imputation was used to address the potential impact of missing data. Each arm was imputed separately and ten imputed datasets were created. We combined data for analysis using Rubin's rules [28]. The same multi-level models previously outlined were then used to analyse the multiply imputed data and to examine cost-effectiveness. A CEAC was generated from the imputed data.
3. Real world running costs. Clinician training is a one-off cost, and once up and running there would be no further costs related to training. Thus the same clinicians could conduct the

intervention on further cohorts of participants without further training. This sensitivity analysis therefore excluded training costs and only considered the running costs of the intervention.

RESULTS

Baseline characteristics for the two arms of the trial are presented in Table 1. Data were collected for 220 participants, of which 109 were in the intervention arm. Arms were well balanced in terms of age, BMI and education. Although not statistically significant, there were notable differences in gender and baseline health utility (0.62 vs 0.66). This is reflected in the baseline resource use and baseline cost data, with the control arm using more health care at baseline than the intervention arm. Thus, it was necessary to control for baseline variables within the economic analysis.

'Table 1 here'

Both arms saw improvements in both utility and RMDQ over time. Mean utility scores in the control arm increased from 0.62 to 0.74, whilst the control arm saw improvements from 0.66 to 0.79. This suggests that both interventions were beneficial to the patient. For the RMDQ, the control arm improved from 10.24 down to 5.97, whilst the intervention arm saw improvement from 9.95 to 3.27 (Table 2).

'Table 2 here'

Intervention and healthcare resource use and costs are shown in Table 3. The biggest drivers of cost related to the intervention itself were training costs to ensure the intervention was implemented correctly. In terms of intervention materials, the intervention is very cheap, owing to the fact that the only extra materials are instructional postcards for intervention participants. The primary cost of the intervention is the physiotherapy care itself, due to the nature of the intervention, it's impossible to disentangle where the ETMI care ends and other physiotherapy appointments begin, thus intervention costs related to ETMI are captured within the healthcare costs.There were lower levels of resource in terms of medication, doctor visits and physiotherapist appointments for the intervention arm compared to the control arm. The most notable difference relates to physiotherapy appointments used: the control arm had on average 5.11 appointments at a cost of 643.62NIS (£105.03) compared to just 3.62 at a cost of 455.72NIS (£74.36) for intervention participants. The baseline and cluster adjusted

cost difference specifically for physiotherapy appointments demonstrated a saving of 191.79NIS (95%CI 289.51, 94.07), this is statistically significant (p=0.00).

'Table 3 here'

The intervention arm was associated with an extra 0.02 QALYs per intervention participant compared to the control arm. Reflecting the QALY results, the condition specific RMDQ demonstrated a reduction in RMDQ score of 2.67 in comparison to the control arm. Incremental costs were higher for the intervention arm, with a cost difference of 230.35NIS (£37.59) per participant. Thus, costs were higher for the intervention arm, but outcomes were better (Table 4).

'Table 4 here'

The net benefit curve intersects the x-axis at approximately 10,000NIS (£1631.85) (Figure 1). This point reflects where NB is equal to zero, and thus approximates the cost per QALY. The lower confidence interval never crosses zero. This suggests that regardless of willingness to pay, there will always be some uncertainty surrounding the result. This reflects the modest intervention effects and the increased costs related to the intervention. The CEAC in Figure 2 shows the probability at different levels of WTP that the intervention is more cost-effective than the control. At very low levels of WTP, the control arm is likely the more cost-effective option, with the intervention just having a 27% chance of being the more cost-effective option at a WTP of 5000NIS (£815.93). As WTP for QALYs rise, the probability of the intervention quickly increases. At a WTP of 20,000NIS (£3263.71) per QALY, there is a 78% chance that the intervention is the more cost-effective option. This rises to 88% by a WTP of 50,000NIS (£8159.27), before stabilising at about 89% for higher WTP levels.

'Figures 1 & 2 here'

Sensitivity Analyses

The adjusted mean change in RMDQ score between the two arms was -2.67 (p=0.000). The CEAC analysis associated with the RMDQ scores found that even at a very low willingness to pay of 100NIS (£16.32) per RMDQ point, there is a 81% chance the intervention is the more cost-effective option. By 200NIS (£32.64), there is a 99% chance the intervention is the more cost-effective option.

The second sensitivity analyses addresses the issue of missing data. Attrition was relatively low with just 14% of SF-6D scores being missing at the final follow up. Multiple imputation of missing data has limited impacts on the results. At a willingness to pay of 50,000NIS (£8159.27) per QALY there is an 85% chance that the intervention is the more cost-effective, only 3% less than the complete case analysis.

The final sensitivity analysis considers the real-world running costs: excluding all costs related to training. In this scenario the intervention is actually costs saving, saving -252.61NIS (95%CI: -381.92 - 123.30) (£41.86) per patient. In this sensitivity analysis the intervention dominates the control arm: it is associated with lower costs and better outcomes.

DISCUSSION

This paper has reported the first cost-effectiveness analysis of an enhanced trans-theoretical model intervention (ETMI) aiming to increase recreational physical activity in patients with chronic low back pain compared to physiotherapy usual care. Echoing the main study findings [8], both trial arms improved, however the intervention arm was associated with better outcomes compared to the usual care arms as measured by the RMDQ, and QALYs. This suggests ETMI may be useful for reducing CLBP, but at what cost? In the 12 months following the intervention, doctor and physiotherapy appointments, as well as medication use, were all comparatively reduced in the intervention arm. Adopting a healthcare perspective, the incremental costs of the intervention were 230.35NIS (£37.59) compared to usual care as training costs outweighed cost savings. This biggest cost driver was training costs for delivery of the intervention. The point estimate of the ICER was 10,645NIS (£1737.11). The uncertainty analysis suggested that at a willingness to pay threshold of 20,000NIS (£3263.71) there was 70% chance the intervention was cost-effective than usual care, this rose to 88% at a willingness to pay of 50,000NIS (£8159.27). No explicit cost-per QALY threshold exists in Israel, it however has been reported that interventions with a cost-per QALY less than 50,000NIS (£8159.27) tend to be approved by the Public Committee [11]. Thus, with a cost-per QALY of 10,645NIS (£1737.11), the ETMI intervention represents good value for money and has a very high probability (88%) of being cost-effective at the implied threshold.

Our primary analysis is very conservative as it assumes all of the training costs are allocated to the limited number of people treated within the trial. If implemented in practice each trained

physiotherapists will treat many more people than just those included in the study. Indeed, it could be argued that it is inappropriate to include any training costs in the model as these will be met elsewhere as part of the normal overall running costs of the service. When considering only the ongoing costs, the ETMI dominated usual care; i.e. it was cheaper and more effective. Regardless of how the training costs are managed in the analyses these data indicate that ETMI is very likely to be cost-effective when compared to usual care and it might even be cost saving. This reflects the findings of a recent review that suggests interventions that combine physical and psychological treatments are more likely to be cost-effective for CLBP [29].

Overall our results were robust to sensitivity analyses, with multiple imputation for missing data having little impact on key results.

There are a number of strengths and limitations associated with the methodology of the study and this analysis. The study is novel in integrating trans-theoretical models of behaviour change into routine physiotherapy appointments. A key strength and limitation of the study relates to the method of recruitment into the study. The recruitment method reflected the real world referral process and nearly all referrals within one geographic district were included. A limitation to this method of recruitment was that participants were allocated to their nearest geographically available physical therapist (the referrer had no knowledge of the physiotherapist's allocation), and thus it cannot claim to be a 'randomised' controlled trial: we cannot rule out selection bias. The use of routine data to collect information on resource use was a strength allowing the collection of detailed data on medication, doctor visits and physiotherapist visits, however a limitation to this approach was that no information on hospital use was collected and key costs potentially could have been missed. The SF-12 was used to capture generic health-related quality of life data and QALYs were derived using the associated utility algorithm [15]. A limitation of this is that the study was conducted in Israel and no Israel specific tariff exists, and preferences for health states may differ to those where the tariff originates. Given one of the prime issues with CLBP is absence from work, and a key goal of treatment for CLBP is to enable return to work, it is a limitation that no data was collected on whether return to work was achieved. Given the comparative improvement within the intervention arm, it is not unreasonable to presume that ability to work would also improve in this arm. This implies that wider productivity gains may have been accrued by the intervention arm that we have failed to capture. The study focused on younger populations, below age 55, and we cannot generalise the effect to older groups. While the

study took place in a single district, it included a wide variety of socio-economic groups, and represents a large section of the Israeli population, which has only 5 districts in total.

The use of ETMI led to fewer medical appointments and fewer medications being necessary. At the same time, outcomes were improved for patients who received the intervention. In summary, the findings within this study are very encouraging and suggests that ETMI is a cost-effective strategy for treating CLBP, at least in younger populations. However there are a range of limitations to this study, combined with a modest sample size (n=220), and as such this should be considered a pilot study for a large scale randomised controlled trial to robustly test the effectiveness and cost-effectiveness of the ETMI intervention.

Contributors: AC conducted the economic analysis and drafted the paper. NB-A was responsible for setting up the trial and conducting the data collection under the supervision and guidance of TP, YS and GC. MU, TP and NB-A contributed to the drafting and editing of the manuscript.

Funding: The study was supported by Maccabi Healthcare Services (an Israeli Public Health organisation)

Competing interests statement: The authors have nothing to disclose.

Data sharing statement: All data requests relating to the ETMI trial should be made to noaba@ariel.ac.il

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TABLES:

Table 1: Baseline Data

		Control Arm			Intervention Arm		
		N	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**
Baseline Characteristics	**Age**	111	42.31	7.15	109	42.37	7.55
	BMI	110	26.11	5.02	108	26.13	4.84
	Years Education	110	14.93	2.68	108	14.45	2.68
	Gender: Male	47	N/A	N/A	54	N/A	N/A
	Gender: Female	64	N/A	N/A	55	N/A	N/A
Baseline health outcomes	**Baseline SF-6D**	107	0.62	0.13	108	0.66	0.14
	RMDQ Score	111	10.24	5.18	109	9.95	4.95
Baseline resource use	**Baseline Number of medications**	111	1.43	1.44	107	1.37	1.50
	Baseline number of doctor visits	111	1.58	1.30	107	1.55	1.29
Baseline costs	**Baseline Medication costs (NIS)**	111	49.83	51.45	106	45.41	53.25
	Baseline doctor appointment costs (NIS)	111	197.07	162.15	107	193.93	161.28

Table 2: Outcome data

SF6D Utility by Arm						
	Control			Intervention		
	Baseline	**3 Months**	**12 Months**	**Baseline**	**3 Months**	**12 Months**
Observations	107	98	95	108	100	94
Mean utility	0.62	0.73	0.74	0.66	0.77	0.79
Standard Deviation	0.13	0.14	0.15	0.14	0.14	0.11
Min	0.37	0.36	0.37	0.38	0.38	0.42
Max	0.94	1	1	1	1	1
RMDQ Score by arm						
	Control			Intervention		
	Baseline	**3 months**	**12 Months**	**Baseline**	**3 Months**	**12 Months**
Observations	111	98	95	109	100	94
Mean RMQ score	10.24	6.83	5.97	9.95	4.73	3.27
Standard Deviation	5.18	5.91	5.51	4.95	4.66	4.45
Min	1	0	0	1	0	0
Max	21	23	21	21	23	22

Table 3: Resource use and costs

Intervention costs (cluster level)						
Component	**Details**	**Resource used**	**Unit cost (NIS)**	**Total cost (NIS)**	**Cost per intervention physiotherapist (NIS)**	**Cost per intervention patient (NIS)**
Physiotherapist training	12 trainees attended: 2 days	192 hours	126 per 30 mins	48384	4398.55	443.89
	Trainers time: 2 days	16 hours	126 per 30 mins	2016	183.27	18.50
Materials	Post cards for physiotherapists	13 per physio	650 total	650	59.09	5.96
			Totals:	51050	4640.91	468.35

Healthcare resource use and cost data (unadjusted)										
	Control Arm					**Intervention Arm**				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Medication used	111	1.60	2.68	0	22	107	1.21	2.11	0	17
Doctor visits	111	1.49	2.47	0	12	107	1.02	1.97	0	17
Physio appointments	111	5.11	3.44	1	18	107	3.62	1.97	1	12
Medication costs (NIS)	111	48.38	80.97	0	595.88	107	39.49	76.50	0	654.02
Doctor costs (NIS)	111	185.81	308.90	0	1500	107	127.34	245.83	0	2125
Physio costs (NIS)	111	643.62	432.94	126	2268	107	455.72	248.19	126	1512

Table 4: Incremental Analysis: Intervention versus control – fully adjusted for baseline, co-variates and clustering

	Mean difference	**Std. Error**	**z**	**P>z**	**95% CI**	**95% CI**
QALYs	0.02	0.01	1.45	0.15	-0.01	0.05
Change from BL RMDQ	-2.67	0.69	-3.85	0.00	-4.03	-1.31
Cost (NIS)	230.35NIS	74.03	3.11	0.002	85.26	375.44
					Cost per QALY	10,645.12NIS
					Cost per RMD point	86.27NIS

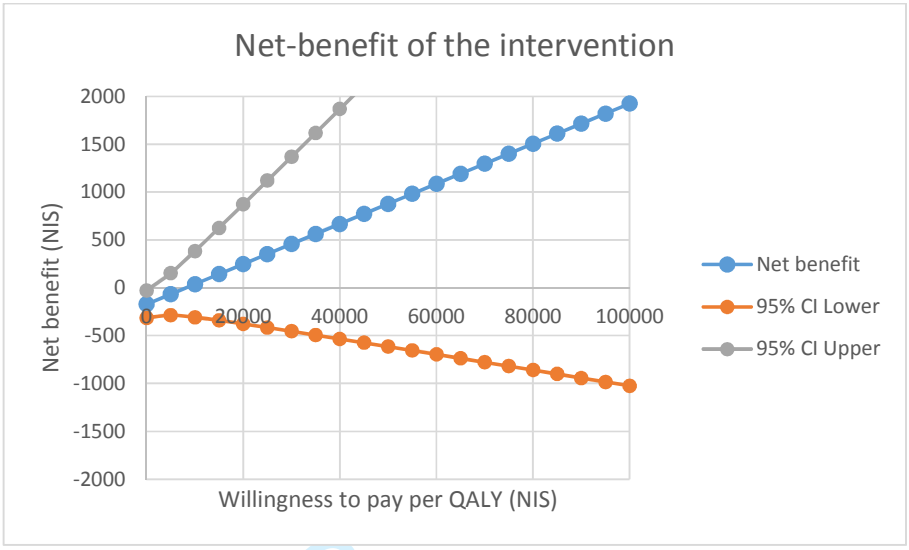

Figure 1: Net-benefit by willingness to pay (NIS) for QALYs

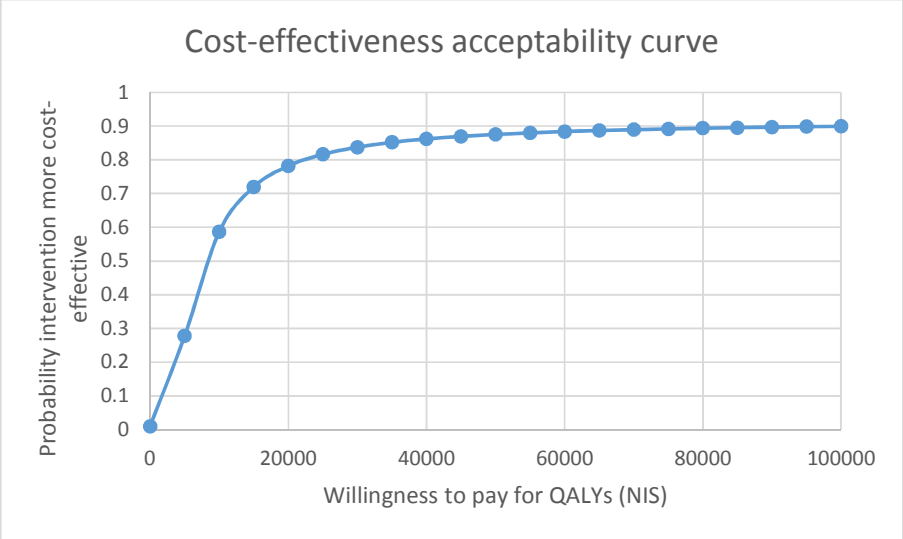

Figure 2: CEAC - probability cost-effective at different levels of willingness to pay (NIS) for QALYs

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No or Line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 2: title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2: Abstract – only partially followed as BMJ Open preferences overruled Cheers format.
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 3: paragraph 1 & 2
		Present the study question and its relevance for health policy or practice decisions.	Page 3: paragraph 1 & 2
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 4: paragraph 2
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 4: paragraph 3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5: paragraph 2
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5: paragraph 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 4: paragraph 1
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 4: paragraph 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5: paragraph 3
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 4: paragraph 3
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 5: paragraph 3
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 5: paragraph 2
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	N/A

Section/item	Item No	Recommendation	Reported on page No or Line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 4: paragraph 1
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 6-8
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Pages 8-9
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Pages 9-10
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	No pre-specified subgroups
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 9: paragraph 3
Other			
Source of funding	23	Describe how the study was funded and the role of	Page 12

Section/item	Item No	Recommendation	Reported on page No or Line No
		the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 12

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

IS AN ENHANCED BEHAVIOUR CHANGE INTERVENTION COST-EFFECTIVE COMPARED TO PHYSIOTHERAPY FOR PATIENTS WITH CHRONIC LOW BACK PAIN? RESULTS FROM A MULTI-CENTRE TRIAL IN ISRAEL

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019928.R1
Article Type:	Research
Date Submitted by the Author:	21-Dec-2017
Complete List of Authors:	Canaway, Alastair; Univesity of Warwick, Clinical Trials Unit Pincus, Tamar; Royal Hollaway University of London, Psychology Underwood, Martin; Warwick University, Warwick Medical School Shapira, Yair; Ariel University, Faculty of Health Sciences Chodick, Gabriel ; Sackler School of Medicine Tel Aviv University, Ramat Aviv, Israel, Epidemiology and Database Research; Maccabi Healthcare Services Ben-Ami, Noa; Ariel University, Faculty of Health Sciences
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Lower back pain, economic evaluation, QALYs, cost-utility analysis, cost-effectiveness analysis, physiotherapy

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Funding: The study was supported by Maccabi Healthcare Services (an Israeli Public Health organisation).

Key words: Lower back pain; economic evaluation; QALYs; cost-utility analysis; cost-effectiveness analysis; physiotherapy

Word count: 3423

ABSTRACT

Objectives: To assess the cost-effectiveness of an enhanced trans-theoretical model of behaviour change in conjunction with physiotherapy compared to standard care (physiotherapy) in patients with chronic lower back pain (CLBP).

Design: Cost-utility and cost-effectiveness analysis alongside a multi-centre controlled trial from a health care perspective with a one year time horizon.

Setting: The trial was conducted in eight centres within the Sharon district, Israel.

Participants: 220 participants aged between 25 to 55 years who suffered CLBP for a minimum of three months were recruited.

Interventions: The intervention used a model of behaviour change that sought to increase the adherence and implementation of physical activity in conjunction with physiotherapy. The control arm received standard care in the form of physiotherapy.

Primary and secondary measures: the primary outcome was the incremental cost per quality adjusted life year (QALY) of the intervention arm compared to standard care. The secondary outcome was the incremental cost per Roland Morris Disability Questionnaire (RMDQ) point.

Results: The cost per QALY point estimate was 10,645NIS (£1737.11). There was an 88% chance the intervention was cost-effective at the 50,000NIS per QALY threshold. Excluding training costs, the intervention dominated the control arm resulting in fewer physiotherapy and physician visits whilst improving outcomes.

Conclusions: The ETMI intervention appears to be a very cost-effective intervention leading to improved outcomes for low cost. Given limitations within this study, there is justification for examining the intervention within a larger long term randomised controlled trial.

Trial registration number: NCT01631344

Word count: 3423

Strengths and limitations of this study:

- Novel intervention that integrates behaviour change theory into physical therapy appointments.
- Health care and medication data was collected via routine data sources providing detailed information on health and medication use.
- Generalisability to the region - recruitment methods reflected actual referral processes with nearly all referrals within the Sharon district being included in the study.
- Due to the recruitment method reflecting reality, selection bias cannot be ruled out.
- No Israel specific SF-6D algorithm exists and thus QALYs will differ if preferences differ between countries.

INTRODUCTION

Lower back pain is the number one cause of daily disability worldwide [1]. It remains highly prevalent and difficult to treat [2]. Increased physical activity is recommended as the most promising and effective approach to treating patients with chronic lower back pain (CLBP) [3]. Evidence suggests that physical activity is effective in improving function, preventing further pain, and improving return to work outcomes [4,5]. However, adherence to advice to start, and maintain higher levels of physical activity is problematic [6,7] with many people failing to continue to exercise in the long term [7]. Criticisms of existing intervention suggest the need for theory driven interventions that focus on the key obstacles to long term rehabilitation [7]. An enhanced trans-theoretical model intervention (ETMI) of behaviour change was developed to address this [8]. ETMI seeks to increase the adherence and implementation of physical activity by harnessing theory–informed counselling, based on behaviour change principles to overcome barriers to exercise. In line with theory, ETMI matches patients' readiness to change with an appropriate consultation style from the practitioner. Additionally, it aims to tackle fear of movement, whilst enhancing reassurance and education about CLBP.

In the primary clinical paper [8], ETMI was found, in an Israeli study, to be more effective than usual physiotherapy as assessed with the Roland-Morris Disability Questionnaire [9] as a primary outcome (2.7 point difference in mean change from baseline). In addition, it performed better on the physical scale of the SF-12 questionnaires [10], worst and average levels of pain, and self-report of levels of physical activity. As well as demonstrating effectiveness, it is important to consider cost-effectiveness of implementing new interventions. In Israel, interventions that have a cost per quality adjusted life year (QALY) less than 50,000 New Israeli Shekels (NIS) tend to be approved by the Public Committee and can therefore be considered cost-effective [11]. In the UK, NICE uses the threshold of £20,000-£30,000 per quality adjusted life year [12] to assess cost-effectiveness. This research takes place within the Israeli context. In this paper we seek to answer the question of whether the ETMI intervention is more cost-effective than usual care for young patients with CLBP.

METHODS

The economic analysis is characterised as a within-trial cost-utility analysis examining the incremental cost per QALY associated with introducing the intervention. The ETMI study was a multi-centred pragmatic controlled trial of patients with CLBP. It is described in detail elsewhere [8]. The trial ran between February 2011, and July 2012. Ethics approval was obtained from both the ethics committee of the Maccabi Healthcare Services (a public health organisation), and Tel Aviv University. Informed consent was mandatory for inclusion within the trial. The trial was registered on clinicaltrials.gov (NCT01631344). This analysis uses a one year time horizon (reflecting the clinical paper), hence costs and outcomes were not discounted. Prices are presented in 2012 terms (the year the trial concluded). Costs are presented in New Israeli Shekels (NIS), with Great Britain Pounds (GBP) in parentheses. The exchange rate from mid-2012 is used to convert NIS to GBP (6.128NIS = £1).

Population

The trial focussed on people aged between 25 to 55 years with CLBP (as defined by a duration of over 3 months) who were referred to the Maccabi Health Services physical therapy clinics within the Sharon district. Older patients were not considered as there is evidence that a trans-theoretical approach to increase compliance in older populations is not effective [13]. All participants were required to speak Hebrew fluently. Patients with the following contraindications were excluded: rheumatic diseases, tumours, fractures, fibromyalgia, previous spinal surgery, pregnancy, post-car (or work) accident pain.

Recruitment and arm allocation

Eight participating centres were recruited. Across the eight centres, 11 physiotherapists administered the intervention, whilst 23 provided normal care. All physios had in excess of four years of experience. All referrals for physiotherapy from general practice or orthopaedic secondary care within the district were allocated by an independent party to the nearest physiotherapist according to geographic location without knowledge of whether the physiotherapist was within the trial. Although not randomised, the allocation of participants was not under the influence of the study team. Upon arriving for treatment, eligibility was assessed and eligible participants were provided with information

about the trial. Those who did not consent were not included in the study and proceeded to receive treatment as usual.

Interventions

The two arms of the trial can be characterised as follows:

1. Usual care (control) – The usual care group received standard physical therapy treatment, this could include: mobilisation, manipulation, back exercises, postural training, attending back school, electrical stimulation, short wave diathermy, cooling, and stretching.
2. With the exception of back exercise, the intervention did not use any of the methods associated within the usual care arm. The main aim of the intervention was to facilitate participation in a chosen recreational physical activity through matching and supporting the patient's cognitive readiness to change, and so, reducing known barriers to physical activity such as low motivation, low self-efficacy, and fear of movement. A semi-standardized protocol was used for the intervention (see supplementary materials); a full exposition of the enhanced intervention can be found in Ben-Ami et al [8].

Resource use and costs

The costing perspective adopted for this study was a health care perspective, wider societal costs were not considered. The healthcare perspective included the cost of training staff to deliver the intervention, the cost of delivering the intervention (including the time and materials used) and healthcare costs. Information on health care use was captured primarily through the computerised medical records that are available through the Maccabi Healthcare Service. These records were used to extract information on physiotherapist appointments, general practitioner appointments and all pain and inflammation medication; this includes over the counter purchases. No data on hospitalisation was captured. Training costs were recorded by the trial team. Unit costs were obtained from the Ministry of Health [14,15]. Resource use was retrospectively collected for the three months prior to the start of the trial to assess baseline resource use, and for the twelve months of follow up. Consequently, information was available for: all physiotherapy appointments; all doctor appointments; all pain and inflammation medication; and the costs associated with setting up and delivering the intervention.

Outcomes

The primary outcome for the economic evaluation was incremental cost per Quality Adjusted Life Years (QALYs) as recommended [16]. QALYs are a unit of outcome that combine both quantity and quality of life into a single metric. QALYs have been widely adopted in many countries around the world (e.g. the National Institute for Health and Care Excellence in the UK [12]). To obtain utility values for QALY calculation within this study, the SF-12 was included at baseline, and both follow ups (3 months and 12 months). The SF-12 is a generic health related quality of life questionnaire examining 12 domains of health [10]. Algorithms exist to convert SF-12 scores into SF-6D utility values [17–19]. As the version 1 (US) SF-12 instrument was used, the appropriate algorithm provided by the University of Sheffield was used to calculate utility values [17–19]. From baseline through the follow ups, these health utilities were combined with length of time information to calculate QALYs. QALYs were calculated using the trapezium rule which calculates the area under the curve [20]. The second outcome considered was the Roland-Morris Disability Questionnaire (RMDQ): a common and well validated back pain specific measure [9,21,22] suitable to this setting which formed the primary outcome in the clinical evaluation of the intervention [8]. The RMDQ is designed to assess disability caused by lower back pain, it contains 24 statements relating to disability caused by back pain (e.g. I can only walk short distances because of my back). Each answer is worth one point resulting in scores between 0 (no disability) to 24 (severely disabled).

Statistical analysis

First, costs and outcomes between the two arms were compared in isolation. They were then combined within a cost-effectiveness analysis which analysed both costs and outcomes simultaneously. Given the hierarchical structure of the data, appropriate statistical methods were required [23]. The primary analysis is a complete case analysis.

Analysis of costs and QALYs

We included relevant characteristics and baseline scores as co-variates within a regression framework to control for baseline differences in characteristic or health states [24–26]. Due to the

clustered nature of the data, it was necessary to use analytic methods that accounted for clustering [23]. Multi-level models were adopted allowing for random effects at the physiotherapist and centre level. Finally, the skewness of the data can affect the method of analysis used. Given the skewed cost data collected in the trial, it was necessary to adopt a method that could handle non-parametric data. Generalized linear models [27] were therefore implemented using a gamma family, and identity link function following tests (data visualisations, modified Park test and 'linktest') to optimise model fit. Thus, the final model was a multi-level generalised linear model controlling for baseline characteristics (including age, gender, body mass index, health state and years of education). This simultaneously addressed the three specified issues relevant to the data. This was implemented within Stata [28] using the 'meglm' code.

Examining cost-effectiveness

An incremental cost-effectiveness ratio can be calculated by dividing the incremental costs by incremental QALYs. A cost per QALY approach however does not reflect that costs and outcomes may be correlated, and does not characterise the uncertainty that is present [26,29]. To address this, we used the net benefit approach which combines costs and QALYs into a single metric of net benefit [30]. The net-benefit approach multiplies QALYs with the willingness to pay (WTP) for those QALYs by the decision maker, and then subtracts costs [30]. This was done for a range of willingness to pay values. To control for clustering, a hierarchical approach was necessary [31]. A multi-level regression framework was therefore used for each WTP level to assess the cost-effectiveness whilst also controlling for baseline imbalances and clustering. Given the parametric nature of net-benefits, a generalised linear model was not required, hence the 'mixed' Stata command was used. Within the model, for any willingness to pay, if the intervention co-efficient (the incremental net benefit) was greater than zero, then the intervention was deemed cost-effective at that willingness to pay. Using data from the output of the net benefit regressions, cost-effectiveness acceptability curves (CEACs) were generated to characterise the uncertainty in decision making at each level of willingness to pay [25,30].

Secondary analysis

Cost per RMDQ point. The analysis methods outlined above were followed, however the outcome of interest was 'difference in RMDQ' score rather than QALYs.

Sensitivity analyses

We ran two further sensitivity analyses:

1. Multiple imputation in Stata for missing data. A fixed effect approach for multiple imputation was used to address the potential impact of missing data. Each arm was imputed separately and ten imputed datasets were created. We combined data for analysis using Rubin's rules [32]. The same multi-level models previously outlined were then used to analyse the multiply imputed data and to examine cost-effectiveness. A CEAC was generated from the imputed data.
2. Real world running costs. Clinician training is a one-off cost, and once up and running there would be no further costs related to training. Thus the same clinicians could conduct the intervention on further cohorts of participants without further training. This sensitivity analysis therefore excluded training costs and only considered the running costs of the intervention.

RESULTS

Baseline characteristics for the two arms of the trial are presented in Table 1. Data were collected for 220 participants, of which 109 were in the intervention arm. Arms were well balanced in terms of age, BMI and education. Although not statistically significant, there were notable differences in gender and baseline health utility (0.62 vs 0.66). This is reflected in the baseline resource use and baseline cost data, with the control arm using more health care at baseline than the intervention arm. Thus, it was necessary to control for baseline variables within the economic analysis.

'Table 1 here'

Both arms saw improvements in both utility and RMDQ over time. Mean utility scores in the control arm increased from 0.62 to 0.74, whilst the control arm saw improvements from 0.66 to 0.79. This suggests that both interventions were beneficial to the patients. For the RMDQ, the control arm

improved from 10.24 down to 5.97, whilst the intervention arm saw improvement from 9.95 to 3.27 (Table 2).

'Table 2 here'

Intervention and healthcare resource use and costs are shown in Table 3. The biggest drivers of cost related to the intervention itself were training costs to ensure the intervention was implemented correctly. In terms of intervention materials, the intervention is very cheap, owing to the fact that the only extra materials are instructional postcards for intervention participants. The primary cost of the intervention is the physiotherapy care itself, due to the nature of the intervention, it is impossible to disentangle where the ETMI care ends and other physiotherapy appointments begin, thus intervention costs related to ETMI are captured within the healthcare costs. There were lower levels of resource in terms of medication, doctor visits and physiotherapist appointments for the intervention arm compared to the control arm. The most notable difference relates to physiotherapy appointments used: the control arm had on average 5.11 appointments at a cost of 643.62NIS (£105.03) per patient compared to just 3.62 at a cost of 455.72NIS (£74.36) per patient for the intervention arm. The baseline and centre adjusted cost difference specifically for physiotherapy appointments demonstrated a saving of 191.79NIS (95%CI 289.51, 94.07), this is statistically significant (p=0.00).

'Table 3 here'

The intervention arm was associated with an extra 0.02 QALYs (95% CI: -0.01, 0.05) per intervention participant compared to the control arm. Reflecting the QALY results, the condition specific RMDQ demonstrated a reduction in RMDQ score of 2.67 (95% CI: -4.03, -1.31) in comparison to the control arm. Incremental costs were higher for the intervention arm, with a cost difference of 230.35NIS (£37.59) per participant (95% CI: 85.26NIS, 375.44NIS). Thus, costs were higher for the intervention arm, but outcomes were better (Table 4).

'Table 4 here'

The net benefit curve intersects the x-axis at approximately 10,000NIS (£1631.85) (Figure 1). This point reflects where NB is equal to zero, and thus approximates the cost per QALY. The lower confidence interval never crosses zero. This suggests that regardless of willingness to pay, there will always be some uncertainty surrounding the result. This reflects the modest intervention effects and

the increased costs related to the intervention. The CEAC in Figure 2 shows the probability at different levels of WTP that the intervention is more cost-effective than the control. At very low levels of WTP, the control arm is likely the more cost-effective option, with the intervention just having a 27% chance of being the more cost-effective option at a WTP of 5000NIS (£815.93). As WTP for QALYs rise, the probability of the intervention quickly increases. At a WTP of 20,000NIS (£3263.71) per QALY, there is a 78% chance that the intervention is the more cost-effective option. This rises to 88% by a WTP of 50,000NIS (£8159.27), before stabilising at about 89% for higher WTP levels.

'Figures 1 & 2 here'

Secondary analysis

The adjusted mean change in RMDQ score between the two arms was -2.67 (p=0.000). The CEAC analysis associated with the RMDQ scores found that even at a very low willingness to pay of 100NIS (£16.32) per RMDQ point, there is a 81% chance the intervention is the more cost-effective option. By 200NIS (£32.64), there is a 99% chance the intervention is the more cost-effective option.

Sensitivity analyses

The first sensitivity analyses addresses the issue of missing data. Attrition was relatively low with just 14% of SF-6D scores being missing at the final follow up. Multiple imputation of missing data has limited impacts on the results. At a willingness to pay of 50,000NIS (£8159.27) per QALY there is an 85% chance that the intervention is the more cost-effective, only 3% less than the complete case analysis.

The second sensitivity analysis considers the real-world running costs: excluding all costs related to training. In this scenario the intervention is actually cost saving, saving -252.61NIS (95%CI: -381.92 - 123.30) (£41.86) per patient. In this sensitivity analysis the intervention dominates the control arm: it is associated with lower costs and better outcomes.

DISCUSSION

This paper has reported the first cost-effectiveness analysis of an enhanced trans-theoretical model intervention (ETMI) aiming to increase recreational physical activity in patients with chronic low back pain compared to physiotherapy usual care. Echoing the main study findings [8], both trial arms improved, however the intervention arm was associated with better outcomes compared to the usual

care arms as measured by the RMDQ, and QALYs. This suggests ETMI may be useful for reducing CLBP, but at what cost? In the 12 months following the intervention, doctor and physiotherapy appointments, as well as medication use, were all comparatively reduced in the intervention arm. Training costs however outweighed these cost savings. This biggest cost driver was training costs for delivery of the intervention. The point estimate of the ICER was 10,645NIS (£1737.11) per QALY. No explicit cost-per QALY threshold exists in Israel, it however has been reported that interventions with a cost-per QALY less than 50,000NIS (£8159.27) tend to be approved by the Public Committee [11]. Thus, with a cost-per QALY of 10,645NIS (£1737.11), the ETMI intervention represents good value for money and has a very high probability (88%) of being cost-effective at the implied threshold. Overall our results were robust to sensitivity analyses, with multiple imputation for missing data having little impact on key results.

Our primary analysis is very conservative as it assumes all of the training costs are allocated to the limited number of people treated within the trial. If implemented in practice each trained physiotherapists will treat many more people than just those included in the study. Indeed, it could be argued that it is inappropriate to include any training costs in the model as these will be met elsewhere as part of the normal overall running costs of the service. When considering only the ongoing costs, the ETMI dominated usual care; i.e. it was cheaper and more effective. Regardless of how the training costs are managed in the analyses these data indicate that ETMI is very likely to be cost-effective when compared to usual care and it might even be cost saving. This reflects the findings of a recent review that suggests interventions that combine physical and psychological treatments are more likely to be cost-effective for CLBP [33].

There are a number of strengths and limitations associated with the methodology of the study and this analysis. The study is novel in integrating trans-theoretical models of behaviour change into routine physiotherapy appointments. A key strength and limitation of the study relates to the method of recruitment into the study. The recruitment method reflected the real world referral process and nearly all referrals within one geographic district were included. A limitation to this method of recruitment was that participants were allocated to their nearest geographically available physical therapist (the referrer had no knowledge of the physiotherapist's allocation), and thus it cannot claim to be a

'randomised' controlled trial: we cannot rule out selection bias. This however should be limited by the fact that each treatment centre contained at least one physio in the intervention arm, and one in the control arm, and those allocating patients to physiotherapists were not aware of which arm each physio was in. Likewise, the sample size is relatively small and is potentially underpowered increasing the uncertainty around results. The use of routine data to collect information on resource use was a strength allowing the collection of detailed data on medication, doctor visits and physiotherapist visits, however a limitation to this approach was that no information on hospital use was collected and key costs potentially could have been missed. Given the intervention arm reported less disability and higher utility scores, it is unlikely the inclusion of such costs would have changed the direction of the results. The Israeli Ministry of Health does not specify a preferred utility measure to generate QALYs [16]. In this study the SF-12 was used to capture generic health-related quality of life data and QALYs were derived using the associated utility algorithm [17]. A limitation of this is that the study was conducted in Israel and no Israel specific tariff exists, and preferences for health states may differ to those where the tariff originates. Furthermore, although the SF-12 is validated and reliable for patients with lower back pain [34], the evidence surrounding the SF-6D is more limited [35] and future studies should explore the use of other utility measures. CLBP by definition is a chronic condition, the one year follow up is therefore a limitation as the long term effectiveness and adherence could not be thoroughly assessed. Given one of the prime issues with CLBP is absence from work, and a key goal of treatment for CLBP is to enable return to work, it is a limitation that no data was collected on whether return to work was achieved. Given the comparative improvement within the intervention arm, it is not unreasonable to presume that ability to work would also improve in this arm. This implies that wider productivity gains may have been accrued by the intervention arm that we have failed to capture. The study focused on younger populations, below age 55, and we cannot generalise the effect to older groups. While the study took place in a single district, it included a wide variety of socio-economic groups, and represents a large section of the Israeli population, which has only six districts in total.

Future research should focus on addressing the limitations within this economic evaluation by conducting a larger scale randomised controlled trial. To comprehensively address limitations a future trial would incorporate the following: larger sample size; using a randomisation procedure to allocate patients to trial arms; include multiple measures of utility specific to the setting; examine the

mechanism of change and long term adherence; and collect resource use information on hospitalisation and wider impacts (e.g. employment).

CONCLUSIONS

The use of ETMI was associated with fewer medical appointments and fewer medications being necessary. At the same time, outcomes were improved for patients who received the intervention. In summary, the findings within this study are very encouraging and suggests that ETMI is a cost-effective strategy for treating CLBP, at least in younger populations with an 88% probability of being more cost-effective than usual care. However there are a range of limitations to this study, combined with a modest sample size (n=220), and as such this should be considered a pilot study for a large scale long term randomised controlled trial to robustly test the effectiveness and cost-effectiveness of the ETMI intervention.

Contributors: AC conducted the economic analysis and drafted the paper. NB-A was responsible for setting up the trial and conducting the data collection under the supervision and guidance of TP, YS and GC. MU, TP and NB-A contributed to the drafting and editing of the manuscript.

Funding: The study was supported by Maccabi Healthcare Services (an Israeli Public Health organisation)

Competing interests statement: The authors have nothing to disclose.

Data sharing statement: All data requests relating to the ETMI trial should be made to noaba@ariel.ac.il

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TABLES:

Table 1: Baseline Data

		Control Arm			Intervention Arm		
		N	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**
Baseline Characteristics	**Age**	111	42.31	7.15	109	42.37	7.55
	BMI	110	26.11	5.02	108	26.13	4.84
	Years Education	110	14.93	2.68	108	14.45	2.68
	Gender: Male	47	N/A	N/A	54	N/A	N/A
	Gender: Female	64	N/A	N/A	55	N/A	N/A
Baseline health outcomes	**Baseline SF-6D**	107	0.62	0.13	108	0.66	0.14
	RMDQ Score	111	10.24	5.18	109	9.95	4.95
Baseline resource use	**Baseline Number of medications**	111	1.43	1.44	107	1.37	1.50
	Baseline number of doctor visits	111	1.58	1.30	107	1.55	1.29
Baseline costs	**Baseline Medication costs (NIS)**	111	49.83	51.45	106	45.41	53.25
	Baseline doctor appointment costs (NIS)	111	197.07	162.15	107	193.93	161.28

Table 2: Outcome data

SF6D Utility by Arm						
	Control			Intervention		
	Baseline	**3 Months**	**12 Months**	**Baseline**	**3 Months**	**12 Months**
Observations	107	98	95	108	100	94
Mean utility	0.62	0.73	0.74	0.66	0.77	0.79
Standard Deviation	0.13	0.14	0.15	0.14	0.14	0.11
Min	0.37	0.36	0.37	0.38	0.38	0.42
Max	0.94	1	1	1	1	1
RMDQ Score by arm						
	Control			Intervention		
	Baseline	**3 months**	**12 Months**	**Baseline**	**3 Months**	**12 Months**
Observations	111	98	95	109	100	94
Mean RMQ score	10.24	6.83	5.97	9.95	4.73	3.27
Standard Deviation	5.18	5.91	5.51	4.95	4.66	4.45
Min	1	0	0	1	0	0
Max	21	23	21	21	23	22

Table 3: Resource use and costs

Intervention costs (cluster level)						
Component	**Details**	**Resource used**	**Unit cost (NIS)**	**Total cost (NIS)**	**Cost per intervention physiotherapist (NIS)**	**Cost per intervention patient (NIS)**
Physiotherapist training	12 trainees attended: 2 days	192 hours	126 per 30 mins	48384	4398.55	443.89
	Trainers time: 2 days	16 hours	126 per 30 mins	2016	183.27	18.50
Materials	Post cards for physiotherapists	13 per physio	650 total	650	59.09	5.96
			Totals:	51050	4640.91	468.35

Healthcare resource use and cost data (unadjusted)										
	Control Arm (missing n = 0)					**Intervention Arm (missing n=2)**				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Medication used	111	1.60	2.68	0	22	107	1.21	2.11	0	17
Doctor visits	111	1.49	2.47	0	12	107	1.02	1.97	0	17
Physio appointments	111	5.11	3.44	1	18	107	3.62	1.97	1	12
Medication costs (NIS)	111	48.38	80.97	0	595.88	107	39.49	76.50	0	654.02
Doctor costs (NIS)	111	185.81	308.90	0	1500	107	127.34	245.83	0	2125
Physio costs (NIS)	111	643.62	432.94	126	2268	107	455.72	248.19	126	1512

Table 4: Incremental Analysis: Intervention versus control – fully adjusted for baseline, co-variates and clustering

	Mean difference	Std. Error	z	P>z	95% CI	95% CI
QALYs	0.02	0.01	1.45	0.15	-0.01	0.05
Change from BL RMDQ	-2.67	0.69	-3.85	0.00	-4.03	-1.31
Cost (NIS)	230.35NIS	74.03	3.11	0.002	85.26	375.44
					Cost per QALY	10,645.12NIS
					Cost per RMD point	86.27NIS

Figures legend

Figure 1: Net-benefit by willingness to pay (NIS) for QALYs

Figure 2: CEAC: probability intervention is cost-effective at different levels of willingness to pay (NIS) for QALYs

1

2

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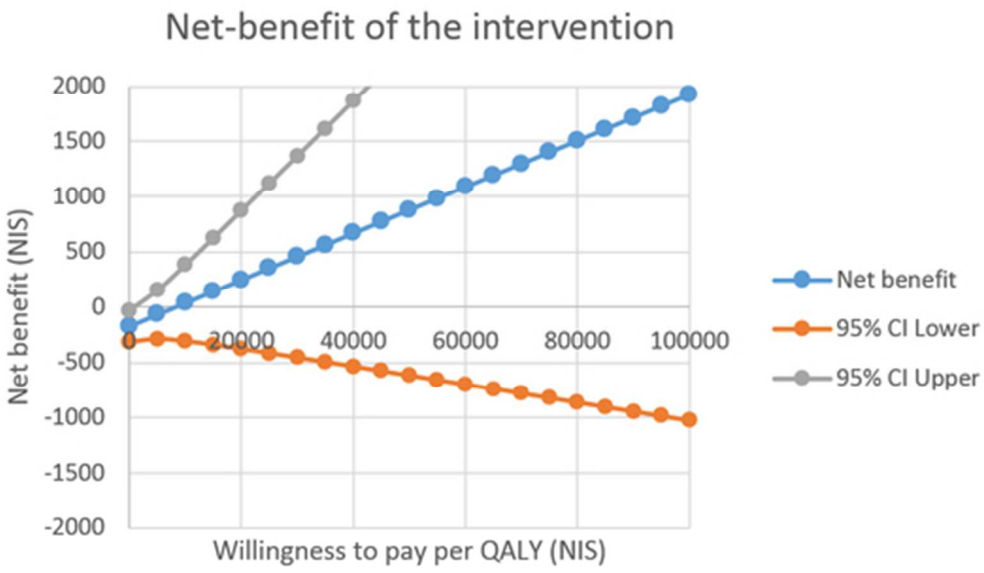

Figure 1: Net-benefit by willingness to pay (NIS) for QALYs

44x26mm (300 x 300 DPI)

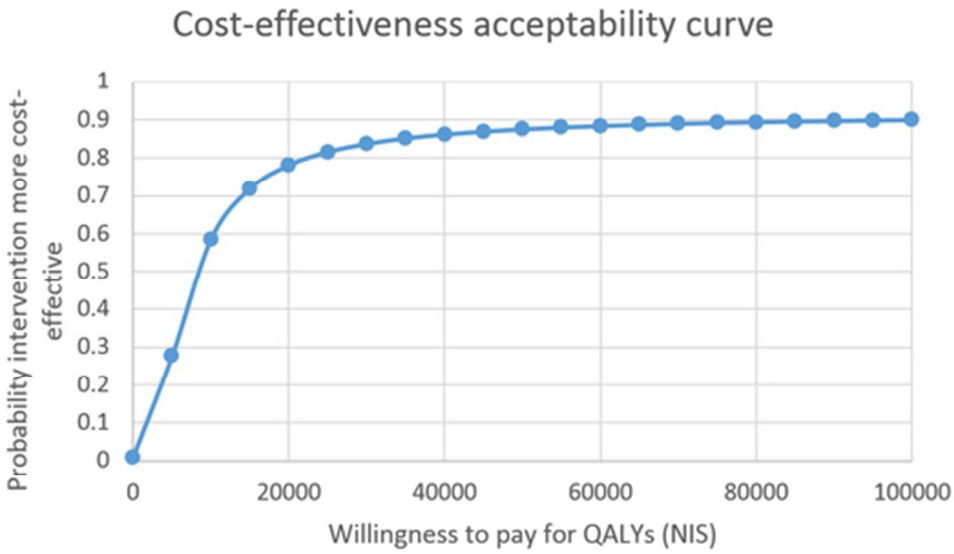

Figure 2: CEAC - probability cost-effective at different levels of willingness to pay (NIS) for QALYs

46x27mm (300 x 300 DPI)

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Standardised protocol:	**Individualised protocol:**	**Classification into stages of change:**
1. Two standard statements were delivered to all patients: a. It is easy to reduce pain. The problem is ensuring that it does not return. b. It is important that the body is strong and flexible. Both statements led to a discussion of the value of physical activity in preventing and managing LBP. 2. Physiotherapists were instructed to use their enhanced skills to build the therapeutic alliance, with an emphasis on communicating empathy and practicing active listening. 3. The following information was delivered to all patients: Physical activity is the most powerful intervention for LBP, and is backed by international research, supported by the WHO. Any aerobic physical activity will do (no prescribed activity). As soon as pain starts, increasing levels of physical activity will help, and that once pain has subside it is important to use the full range of movements, e.g. both flexion and extension. 4. Postcard with exercises.	1. Matching stages of change: a. Use of set criteria[a] to establish stage of change. b. Adapting the process of the intervention to match stage of change. Specifically: Contemplators: Focus on increasing awareness, pros and cons verbalised by patient, physiotherapist neutral. Preparation: (1) specific commitments to engage in physical activity (when, where, how); (2) communicating the commitment to others, and, (3) agreeing level of effort and coaching in healthy walking. c. In the next consultation, for those who failed to carry out their commitment, use of a set of questions based on self-efficacy as specified by Miller & Rollnick in Motivational Interviewing (MI)[b]. If responses score low, change routine to be extremely easy. 2. For those who feared walking and said it increased their pain[1], the physiotherapists used exposure through speed walking in the physiotherapy setting, down a corridor.	Pre contemplation- patients explicitly express unwillingness or reluctance to engage in physical exercise. Contemplation- Patients expresses a willingness to discuss change but does not set a plan/a time to effect change in the immediate 6 months. Preparation- Patients express a plan to implement change within one month. Action- patients reports that they have engaged in physical activity at least 3 times a week on a regular basis for less than 6 months. Maintenance- patients report that they have engaged in physical activity at least 3 times a week on a regular basis for longer than 6 months. Typical work in the contemplation stage involved discussions and evaluation of the proposed action, its effect on others, raised awareness of emotions, and contemplation of a changing self-image. Preparation involved making a commitment, planning for social support and substituting unhealthy conditioning.

a) Singer EA. The Transtheoretical model and primary care: "the times they are a changing". J Am Acad Nurse Pract 2007; 19:4-11

b) Motivational Interviewing: Preparing People to Change Addictive Behavior. New York, NY: The Guilford Press; 1992

1) This component only applied to patients who chose walking as their activity, but failed to engage in it due to fear of pain. Physical therapists specifically asked about engagement and reasons for not engaging in the chosen activity.

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No or Line No (On the tracked version copy!).
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1: title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2: Abstract – only partially followed as BMJ Open preferences overruled Cheers format.
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 3: line 30
		Present the study question and its relevance for health policy or practice decisions.	Page 3: L25-30, P4 L1-2
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 4: paragraph 3
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5 L23- P6 L3, Page 6 L10
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5: L24 – P6 L7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5: paragraph 2 and supplementary materials
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 4: L13
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 4: L14
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 6 L9-26
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 4: paragraph 2, 3, also references the clinical paper which explains in detail.
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 6: paragraph 2
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 5: paragraph 3
	13b	*Model-based economic evaluation:* Describe	N/A

Section/item	Item No	Recommendation	Reported on page No or Line No (On the tracked version copy!).
		approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 4: paragraph 2
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 7-8
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Pages 9-10
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Pages 10-11
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	No pre-specified subgroups
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the	Pages 11-13

Section/item	Item No	Recommendation	Reported on page No or Line No (On the tracked version copy!).
		findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 14
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 14

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist