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A guided and unguided internet- and mobile-based intervention for chronic pain: health economic evaluation alongside a randomised controlled trial

Sarah Paganini,[1,2] Jiaxi Lin,[1] Fanny Kählke,[3] Claudia Buntrock,[3] Delia Leiding,[4] David D Ebert,[3] Harald Baumeister[5]

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For numbered affiliations see end of article.

Correspondence to
Sarah Paganini;
sarah.paganini@sport.uni-freiburg.de

ABSTRACT

Objective This study aims at evaluating the cost-effectiveness and cost-utility of a guided and unguided internet-based intervention for chronic pain patients ($ACTonPain_{guided}$ and $ACTonPain_{unguided}$) compared with a waitlist control group (CG) as well as the comparative cost-effectiveness of the guided and the unguided version.

Design This is a health economic evaluation alongside a three-arm randomised controlled trial from a societal perspective. Assessments were conducted at baseline, 9 weeks and 6 months after randomisation.

Setting Participants were recruited through online and offline strategies and in collaboration with a health insurance company.

Participants 302 adults (≥18 years, pain for at least 6 months) were randomly allocated to one of the three groups ($ACTonPain_{guided}$, $ACTonPain_{unguided}$, CG).

Interventions ACTonPain consists of seven modules and is based on Acceptance and Commitment Therapy. $ACTonPain_{guided}$ and $ACTonPain_{unguided}$ only differ in provision of human support.

Primary and secondary outcome measures Main outcomes of the cost-effectiveness and the cost-utility analyses were meaningful change in pain interference (treatment response) and quality-adjusted life years (QALYs), respectively. Economic evaluation estimates were the incremental cost-effectiveness and cost-utility ratio (ICER/ICUR).

Results At 6-month follow-up, treatment response and QALYs were highest in $ACTonPain_{guided}$ (44% and 0.280; mean costs = €6,945), followed by $ACTonPain_{unguided}$ (28% and 0.266; mean costs = €6,560) and the CG (16% and 0.244; mean costs = €6,908). $ACTonPain_{guided}$ vs CG revealed an ICER of €45 and an ICUR of €604. $ACTonPain_{unguided}$ dominated CG. At a willingness-to-pay of €0 the probability of being cost-effective was 50% for $ACTonPain_{guided}$ (vs CG, for both treatment response and QALY gained) and 67% for $ACTonPain_{unguided}$ (vs CG, for both treatment response and QALY gained). These probabilities rose to 95% when society´s willingness-to-pay is €91,000 ($ACTonPain_{guided}$) and €127,000 ($ACTonPain_{unguided}$) per QALY gained. $ACTonPain_{guided}$ vs $ACTonPain_{unguided}$ revealed an ICER of €2,374 and an ICUR of €45,993.

Conclusions Depending on society´s willingness-to-pay, ACTonPain is a potentially cost-effective adjunct to established pain treatment. $ACTonPain_{unguided}$ (vs CG) revealed lower costs at better health outcomes. However, uncertainty has to be considered. Direct comparison of the two interventions does not indicate a preference for $ACTonPain_{guided}$.

Trial registration number DRKS00006183.

Strengths and limitations of this study

- This is the first study evaluating the (comparative) cost-effectiveness of a guided and an unguided internet-based intervention for individuals with chronic pain.
- In this study state-of-the-art statistical methods such as seemingly unrelated regression equations models or non-parametric bootstrapping techniques were applied.
- Results should be interpreted cautiously, as the study was not powered to statistically test health economic differences.
- No conclusions regarding the long-term cost-effectiveness can be drawn due to the 6-month follow-up period.

BACKGROUND

Chronic pain is highly prevalent[1–4] and associated with substantial decreases in quality of life[1 5 6] as well as high economic costs for society.[3 7–9] Evidence supports psychological interventions as one approach for effectively treating patients with chronic pain.[10] Treatment based on cognitive-behavioural therapy (CBT) or third-wave therapies, like the Acceptance and Commitment Therapy (ACT, a particular form of CBT) have been shown to be effective for chronic pain patients[11 12] and could show acceptable results concerning cost-effectiveness.[13] However, accessibility and availability of treatment are often restricted and up to 40% of individuals with chronic pain do not receive adequate pain treatment.[1 14] Internet- and mobile-based interventions (IMIs) are an effective,

acceptable and feasible way for providing psychological interventions.[15 16] IMIs for chronic pain have been shown to effectively improve pain interference compared with different control groups, such as standard (medical) care, text-based material and mostly waitlist control condition (pooled standardised mean differences (SMD) between 0.4 and 0.5[17 18]).

IMIs can not only facilitate access to psychological treatment, they also have the potential to reduce treatment costs,[19 20] particularly by saving therapist resources. IMIs can be delivered as guided or unguided self-help interventions, with both versions usually requiring less therapist time compared with traditional on-site therapies.[21] A relevant healthcare policy question is which amount of human support is needed in order to improve patient's health. Several studies have demonstrated higher effect sizes for guided IMIs than for unguided IMIs.[21 22] However, as unguided IMIs can be delivered at lower costs per participant, they might as well be an attractive option particularly given their high scalability on a population level.

To the best of our knowledge no randomised controlled trial (RCT) has investigated the (comparative) cost-effectiveness of a guided and an unguided IMI for chronic pain. However, Boer and colleagues found that an IMI for chronic pain was cost-effective compared with a face-to-face group intervention (concerning a one-point-improvement in a pain catastrophising scale).[23] Lin and colleagues recently finalised a three-arm RCT comparing a guided and an unguided version of an IMI based on ACT for chronic pain (ACTonPain$_{guided}$ and ACTonPain$_{unguided}$) against a waitlist control group (CG).[24 25] Compared with the CG, ACTonPain$_{guided}$ showed significantly lower pain interference at 9 weeks and 6 months after randomisation (d=0.58). Differences between ACTonPain$_{unguided}$ and the CG and between both ACTonPain groups were not statistically significant.[25]

The present paper provides results of the cost-effectiveness and cost-utility analysis of ACTonPain$_{guided}$ and ACTonPain$_{unguided}$ compared with a waitlist control group (CG) as well as the comparative cost-effectiveness of ACTonPain$_{guided}$ and ACTonPain$_{unguided}$.

METHODS

Study design and sample

This health economic evaluation was conducted with a 6-month time horizon from the societal perspective alongside a three-arm RCT to investigate the cost-effectiveness and cost-utility of ACTonPain. Full details of the trial design can be found in the study protocol and the main outcome paper of this trial.[24 25] The economic evaluation was conducted and reported in agreement with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[26] and the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) guidelines.[27]

In total, 302 participants were recruited from October 2014 to August 2015 in German pain units, large-scale organisations for chronic pain (e.g. self-help groups), via websites and with assistance of a German health insurance company. Inclusion criteria were (1) adults older than 18 years of age, (2) chronic pain for at least 6 months with (3) considerable intensity (at least Grade II in the Chronic Pain Grade[28]), (4) being medically suitable for participation in a chronic pain IMI, (5) sufficient knowledge of the German language, (6) sufficient computer and internet literacy and (7) having internet access. Exclusion criteria were (1) cancer-related pain, (2) ongoing or planned psychological pain intervention within the forthcoming 3 months and (3) elevated risk of suicide.

Randomisation

All eligible participants who provided informed consent were asked to fill out the baseline assessment and were randomly allocated to one of the three conditions ACTonPain$_{guided}$, ACTonPain$_{unguided}$ and waitlist control group (CG). Permuted block randomisation with variable block sizes (6, 9, 12) was performed by an independent researcher not otherwise involved in the study using an automated, web-based randomisation programme.

Interventions

ACTonPain is a German adaption of an IMI by Buhrman and colleagues[29] for individuals suffering from chronic pain. The intervention is based on ACT and consists of seven modules which include information, metaphors, assignments and mindfulness exercises. Both treatment conditions differ only in the provision of guidance. Participants were advised to work on one module per week (~60 min). In both intervention groups, participants had the option to receive daily automated text messages that repeated content, reminded and motivated participants.

In ACTonPain$_{guided}$ trained and supervised eCoaches (psychologists) provided written feedback for each module, which aimed at increasing participants' motivation and adherence. The total time of an eCoach spent per participant was approximately 1.75 hours. Participants in the CG received the offer to use ACTonPain$_{unguided}$ after the last follow-up assessment. Participants of all three trial arms had unrestricted access to care-as-usual.

Outcome measures

Assessment took place at baseline (T0), post-treatment (T1; 9 weeks after randomisation) and 6-month follow-up (T2; 6 months after randomisation). Outcomes were assessed via an online self-report assessment using a secured internet-based platform (AES, 256-bit encrypted).

Treatment response

The main clinical outcome in the cost-effectiveness analysis was treatment response. This outcome was not defined in the protocol paper. However, it was chosen to calculate a reliable and meaningful change in pain interference according to the recommendations of the Initiative on

Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[30] .

According to the IMMPACT recommendations, clinically important changes were identified with a combination of a distribution-based approach (Pain Interference Scale of the Multidimensional Pain Inventory; MPI[31 32]) and an anchor-based approach (Patient Global Impression of Change scale; PGIC[33]).[30] First, participants with a change of 0.6 points (based on the scale's SD) on the Pain Interference Scale of the MPI (range of the scale: 0–6) were identified as having minimal clinically important changes.[30] Second, participants were identified, which rated their global improvement in the PGIC as 'minimally, much or very much improved'. Participants who fulfilled both criteria were classified having achieved a clinically important change,[30] defined as 'treatment response'.

Quality-adjusted life years

The clinical outcome in the cost-utility analysis was quality-adjusted life years (QALYs) based on the AQoL-8D[34] in the main analysis and the EQ5D-3L[35] in the sensitivity analysis. Utility scores are derived by a preference-based measure of quality of life that is normed by the value 1 meaning perfect health or no restriction in quality of life and 0 meaning a quality of life considered to be not better than death.[36]

The AQoL-8D comprises 35 items, which load on three physical (independent living, pain, senses) and five psycho-social (mental health, happiness, coping, relationships, self-worth) dimensions.[34] The utility scores are scaled by SPSS algorithm for AQoL-8D utility model.[34] The AQoL-8D has been shown to be a reliable and valid instrument, suitable when psychosocial elements of health are the focus of research.[34] Utility weights are derived from the Australian adult population.[37]

The EQ5D-3L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which is rated as causing 'no', 'some' or 'extreme problems,' and is a well validated instrument.[35 38 39] Theoretically, the EQ5D-3L generates 243 different health states. Utility scores were calculated using the UK tariffs.[40]

The AQoL-8D covers more dimensions that might be affected by chronic pain and shows a higher sensitivity to mental health-related quality of life dimensions[41] compared with the EQ5D-3L. Subsequently, and different to our protocol, this instrument was chosen for the main analyses.[24]

QALY health gains for the 6-month period were estimated by calculating the area under the curve (AUC) of linearly interpolated AQoL-8D and EQ5D-3L utility scores.[42]

Resource use and costing

The Trimbos and iMTA questionnaire for costs associated with psychiatric illness (TiC-P)[43 44] was adapted to the German healthcare system and to the healthcare use of individuals with chronic pain. It was used to assess the direct and indirect costs of the past 3 months at T0 and T2. Costs were expressed in Euros (€) for the reference year 2015 (index factor 1.003 and 1.01 for outpatient medical service, respectively) referring to the German consumer price index[45] (for the list of unit cost prices, see table 1). To calculate the 6-month accumulated per-participants costs, the AUC method was used by linearly interpolating 3-month costs (measured at T0 und T2) to cover the full period of 6 months.[42]

$$AUC = \left(\frac{\frac{Costs\ T0}{3} + \frac{Costs\ T2}{3}}{2} \right) * 3 + Costs\ T2$$

Direct medical costs

Healthcare costs (e.g. outpatient and inpatient care) were calculated according to the German guideline of Bock and colleagues.[46 47] The costs of therapeutic appliances (that were not listed in Bock and colleagues[46 47]) and medication were obtained from the Lauer-Taxe, a German encyclopedia for pharmaceutical professional groups and medical and health insurances.[48]

Patient and family costs

Self-reported out-of-pocket expenses and direct non-medical costs (travel expenses, opportunity costs, domestic help) were assessed. Participants reported the costs of travelling by bus or taxi. If not stated, each kilometre was valued at €0.30. Opportunity costs (e.g. time spent at the practitioners waiting room) were estimated at €21.77 per hour. Costs of informal care were valued using a shadow price of €18.97 per hour.[47]

Indirect costs

Indirect costs included productivity losses caused by absenteeism and presenteeism. Absenteeism costs were calculated according to the human capital approach.[49] Self-reported lost work days were multiplied by the corresponding gross average of participants' income per day. To calculate presenteeism costs, participants reported the number of days of reduced efficiency at work. These days were weighted by an inefficiency score. Productivity losses from unpaid work (e.g. domestic help from family members) were valued using a shadow price of €18.97 per hour.[47]

Intervention costs

Intervention costs of ACTonPain$_{guided}$ (€299) and ACTonPain$_{unguided}$ (€69) were based on actual market prices for (un)guided IMIs with a similar amount of modules that contain all costs for developing and hosting the intervention (https://geton-institut.de/).

Statistical analysis

This study was not powered to statistically test differences in health economic outcomes. Therefore, we took a probabilistic decision-making approach for health economic inferences,[50] which aims at informing decision makers on probabilities rather than statistical significance. There

Table 1 List of unit cost prices

Sector	Unit	Category	2015 (in Euro)
Outpatient medical service/ outpatient sector	Euro/contact	Physician	20.81
		Gynaecologist	31.62
		Orthopaedist	25.82
		Specialists for internal medicine	64.25
		Ophthalmologist	36.96
		Dermatologist	19.58
		ENT specialist	28.12
		Surgeon	44.59
		Urologist	25.2
		Neurologist	47.02
		Psychotherapist	79.42
		Dentist	55.24
Remedies	Euro/contact	Logopedics/speech therapy	41.02
		Physiotherapy	17.5
		Ergotherapy/occupational therapy	39.45
		Podiatry/podology	29.13
		Mean remedies	31.77
Hospitals	Euro/day	Completely stationary normal ward	648.11
		Completely stationary intensive care	1,424.60
		Completely stationary psychiatry	348.26
		Semi-stationary general hospital	421.27
		Semi-stationary psychiatry	226.37
Rehabilitation	Euro/day	Outpatient	49.43
		Inpatient	138.19
Opportunitiy costs	Euro/hour	Opportunity costs (leisure time)	21.77
		Opportunity costs (work)	31.89
		Substitution costs for informal care	18.97

Prices for outpatient medical service/outpatient sector were calculated for the year 2013, all other prices for the year 2014[46 47] and adjusted by the German consumer price index for 2015.[45]
ENT specialist, Ear, nose and throat specialist.

was no need to discount costs or outcomes as the time frame for the study was 6 months.

All analyses were conducted according to the intention-to-treat principle. All participants completed T0. Missing clinical outcome data was imputed using the expectation maximisation algorithm in the Statistical Package for the Social Sciences (SPSS, V.20). Analyses of clinical outcomes were conducted and reported elsewhere[25] in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement.[51]

Missing cost data was imputed using the regression imputation procedure in Stata V.13.[52] Predictors of cost data and dropout were identified by logistic regression analysis and were used to obtain the most likely values of the missing cost data. At baseline, AQoL-8D utilities differed between groups ($ACTonPain_{guided}$: M=0.496, SD=0.16; $ACTonPain_{unguided}$: M=0.485, SD=0.17; CG: M=0.463, SD=0.14). Therefore, baseline adjustments were made in further calculations.

We tested group differences in treatment response using the χ^2 test and the Kruskall-Wallis test for QALYs followed by post-hoc comparisons (Bonferroni and Dunn's test, respectively).

In the cost-effectiveness analyses, the outcome estimates were the incremental cost-effectiveness and cost-utility ratio (ICER/ICUR). Incremental costs over the 6-month period were divided by incremental effects (treatment response or QALYs, respectively): $ICER/ICUR=(Costs_{IG}–Costs_{CG})/(Effects_{IG}–Effects_{CG})$ subscripted with IG for the two intervention groups and CG for the comparison groups. Different to the protocol,[24] ICERs/ICURs were reported for 6-month follow-up and not based on post-treatment assessment. As participants were asked for their healthcare utilisation during the last 3 months,

the TiC-P can only be evaluated appropriately at T0 and T2 (as T1 assessments were conducted 9 weeks after randomisation).

Non-parametric bootstrapping by resampling patient-level data with 5,000 replications was used to consider the sampling uncertainty of the ICER/ICUR estimates. Seemingly unrelated regression equations models were bootstrapped to allow for correlated residuals of the cost and effect equations. Bootstrapping was used to obtain 95% CIs based on the percentile method, since parametric techniques are inappropriate for use on skewed variables and ratios.[50]

The bootstrapped ICERs/ICURs were plotted on a cost-effectiveness plane. In addition, a cost-effectiveness acceptability curve was graphed to demonstrate the probabilities of the intervention being cost-effective given varying willingness-to-pay (WTP) ceilings. In order to increase readability of the direct comparison of ACTonPain$_{guided}$ vs ACTonPain$_{unguided}$ the inverse cost-effectiveness acceptability curve (ACTonPain$_{unguided}$ vs ACTonPain$_{guided}$) was additionally plotted. All analyses were performed using Stata V. 13.[52]

Sensitivity analysis

We tested the robustness of outcomes of the main analysis in a sensitivity analysis. We used the EQ5D-3L as a widely used instrument for calculating QALYs. As EQ5D-3L utilities differed between groups at baseline (ACTonPain$_{guided}$: *M*=0.469, *SD*=0.32; ACTonPain$_{unguided}$: *M*=0.436, *SD*=0.31; CG: *M*=0.494, *SD*=0.3). Baseline adjustment was made in the sensitivity analyses.

Patient and public involvement

No patients or public were involved in developing the research question or defining outcome measures, nor were they involved in developing plans for the design or implementation of the study. Negative effects as well as the satisfaction with the intervention were assessed (for results, see Lin and colleagues[25]). Results will be disseminated to those study participants who wished to be notified.

RESULTS

Sample characteristics

The overall sample size was 302. The study dropout rate was 25.8% at 6-month follow-up (ACTonPain$_{guided}$: 33/100; ACTonPain$_{unguided}$: 35/101; CG: 10/101). At 6-month follow-up, dropout rates differed significantly between groups ($\chi^2(2)=20.17$, p<0.001). Pairwise comparison revealed significant differences for ACTonPain$_{guided}$ vs CG ($t(1)=-3.85$, p<0.001) and ACTonPain$_{unguided}$ vs CG ($t(1)=-4.14$, p<0.001). Study dropout was not associated with baseline pain interference or socio-demographic variables.

The average participant was female, 52 years of age, with an above average level of education, employed and had pain treatment in the past. Detailed participants' characteristics and the CONSORT flowchart are reported elsewhere.[25]

Table 2 Treatment response and quality-adjusted life year (QALY) outcomes and group differences at 6-months follow-up

	ACTonPain$_{guided}$ (n=100)	ACTonPain$_{unguided}$ (n=101)	Waitlist control group (n=101)	Test statistic		
	Mean (SD)	Mean (SD)	Mean (SD)	χ^2 (df=2)	Post-hoc test*:	P value
Treatment response (pain interference)	0.44 (0.05)	0.277 (0.04)	0.158 (0.04)	19.44†		<0.001
ACTonPain$_{guided}$ vs CG					*t*(1)=4.52	<0.001
ACTonPain$_{unguided}$ vs CG					*t*(1)=1.91	0.17
ACTonPain$_{guided}$ vs ACTonPain$_{unguided}$					*t*(1)=2.61	0.03
QALY AQoL-8D	0.280 (0.08)	0.266 (0.09)	0.244 (0.08)	9.45‡		0.009
ACTonPain$_{guided}$ vs CG					*Z*=−3.07	0.003
ACTonPain$_{unguided}$ vs CG					*Z*=−1.61	0.16
ACTonPain$_{guided}$ vs ACTonPain$_{unguided}$					*Z*=−1.47	0.21
Sensitivity analysis EQ5D-3L	0.274 (0.12)	0.255 (0.12)	0.253 (0.13)	2.17‡		0.34

CG, waitlist control group; SD, standard deviation; df, degrees of freedom; QALY, quality-adjusted life year.
*Post-hoc test for treatment response: Bonferroni pairwise comparison; Post-hoc test for QALY: Dunn´s test.
†χ^2 test.
‡Kruskall-Wallis H test.

Outcomes

Table 2 shows treatment response and QALY outcomes as well as group differences. At 6-month follow-up, treatment response differed significantly between groups ($ACTonPain_{guided}$: 44/100; $ACTonPain_{unguided}$: 28/101; CG: 16/101). Pairwise comparison revealed significant differences for $ACTonPain_{guided}$ vs CG and $ACTonPain_{guided}$ vs $ACTonPain_{unguided}$ but not for $ACTonPain_{unguided}$ vs CG. Between-group differences in AQoL-8D QALY gains were statistically significant. Pairwise comparison revealed significant differences only for $ACTonPain_{guided}$ vs CG. Incremental EQ5D-3L QALY gains did not differ significantly between study groups.

Costs

At baseline, mean total costs were €3,233 in $ACTonPain_{guided}$, €3,724 in $ACTonPain_{unguided}$ and €3,570 in the CG. The 6-month accumulated per-participants costs by study condition are presented in table 3. $ACTonPain_{guided}$ showed the highest mean total costs (€6,945), followed by the CG (€6,908) and $ACTonPain_{unguided}$ (€6,560). Mean direct costs were the highest in '$ACTonPain_{guided}$' followed by $ACTonPain_{unguided}$ and the CG. The reverse order was found for the indirect costs. Medication, domestic help and opportunity costs were the major cost drivers. Productivity losses produced the highest cost differences between the intervention groups and the CG: -€871 ($ACTonPain_{guided}$ vs. CG) and -€721 ($ACTonPain_{unguided}$ vs. CG).

Health economic evaluation

Table 4 shows the incremental costs, effects and cost-effectiveness and cost-utility ratios (ICER/ICUR) for the main analysis and the sensitivity analysis.

Cost-effectiveness

The cost-effectiveness planes and acceptability curves, representing the 5,000 bootstrap replications, are shown in figures 1A–C and 2A,B. $ACTonPain_{guided}$ showed the same and $ACTonPain_{unguided}$ showed a higher potential of being cost-effective compared with the CG at a WTP of €0 ($ACTonPain_{guided}$: 50%, $ACTonPain_{unguided}$: 67%). The probability of $ACTonPain_{guided}$ being more cost-effective compared with the CG increased to 70% at a WTP of €1,738 and to 95% at a WTP of €6,490 for an additional treatment response. The probability of $ACTonPain_{unguided}$ being cost-effective compard with the CG increased to 70% at a WTP of €660 and to 95% at a WTP of €13,460.

The probability of $ACTonPain_{guided}$ being more cost-effective than $ACTonPain_{unguided}$ was 35% at a WTP of €0 for an additional treatment response. When society's WTP increases up to €5,535 or €17,170 this probability rises to 70% or 95%, respectively. The breakeven point ($ACTonPain_{guided}$ and $ACTonPain_{unguided}$ have the same probability of being cost-effective at same costs) is at €2,188 (see figure 2B).

Cost-utility

Cost-effectiveness planes and acceptability curves that refer to cost-utility are shown in figures 1D–F and 2C,D. $ACTonPain_{guided}$ showed the same and $ACTonPain_{unguided}$ showed a higher probability of being cost-effective compared with the CG at a WTP of €0 (50% and 67%, respectively). The guided interventions' probability of being more cost-effective compared with the CG increased up to 70% and to 95% at a WTP of €24,415 and €91,000, respectively. For $ACTonPain_{unguided}$ these values were €6,130 (70%) and €127,000 (95%) per QALY gained. The probability for $ACTonPain_{guided}$ being more cost-effective than $ACTonPain_{unguided}$ was 35% at a WTP of €0 for one additional QALY. When society's WTP increases up to €113,550, this probability rises to 70% and stagnates on this level. The breakeven point is at €41,350 (see figure 2D).

Sensitivity analysis

Using the EQ5D-3L resulted in larger incremental QALY gains in all comparisons compared with the results using the AQoL-8D (see table 4).

At a WTP of €0, the probability of $ACTonPain_{guided}$ of being cost-effective compared with the CG was 50%. The probability of $ACTonPain_{unguided}$ of being cost-effective compared with the CG was 67% at a WTP of €0. $ACTonPain_{guided}$ vs $ACTonPain_{unguided}$ resulted in a probability of being cost-effective of 35% at a WTP of €0.

DISCUSSION

Comparing both ACTonPain interventions with the CG and by taking uncertainty into account, $ACTonPain_{unguided}$ can be judged as a potentially cost-effective intervention as it dominates the CG by leading to higher QALY gains and more individuals with a treatment response at lower costs.

However, when assuming that an intervention should reach a likelihood of being cost-effective of 95% or greater, it has to be considered that the WTP would have to be €13,460 for treatment response and €127,000 for a QALY gain. Therefore, the judgement of whether the intervention is cost-effective or not ultimately depends on the society's WTP for treatment response or a QALY gained, respectively. $ACTonPain_{guided}$ reveals better results in the main outcome parameters, but at (slightly) higher costs with an ICER of €45 and an ICUR of €604. The probability of being cost-effective at a WTP of €0 compared with the CG is higher in '$ACTonPain_{unguided}$' for both, treatment response and QALYs gained (67%) than in $ACTonPain_{guided}$ (50%).

However, when comparing the costs that would have to be invested by using $ACTonPain_{guided}$ (compared with the CG) for a QALY gained (€604) to the only official WTP threshold stated by the National Institute for Health and Clinical Excellence (NICE) of £20,000 to £30,000[53] (~€22,647 - €33,971; conversion according to the European Central Bank[54]), this intervention would

Table 3 Six-month accumulated per-participants costs (in €) by condition (based on intention-to-treat, n=302)

	ACTonPain$_{guided}$ (n=100)		ACTonPain$_{unguided}$ (n=101)		Waitlist control group (n=101)		Incremental costs		
							Difference, €		
	Mean, €	(SD)	Mean, €	(SD)	Mean, €	(SD)	ACTon Pain$_{guided}$ vs CG	ACTon Pain$_{unguided}$ vs CG	ACTon Pain$_{guided}$ vs ACTon Pain$_{unguided}$
Intervention	299	(–)	69	(–)	0	(–)	299	69	230
Direct medical costs									
Healthcare costs									
Medical specialist	576	(478)	511	(381)	511	(382)	65	0	65
Mental healthcare	212	(431)	181	(397)	258	(455)	–46	–77	31
Other medical specialist*	369	(515)	357	(435)	406	(576)	–37	–49	12
In-patient care (hospital)	198	(479)	173	(369)	141	(420)	57	32	25
Day care	147	(687)	122	(381)	306	(1,584)	–159	–184	25
Rehabilitation	190	(794)	134	(507)	191	(773)	-1	–57	56
Medication	1,092	(2,748)	784	(1,438)	660	(1,638)	432	124	308
Therapeutic appliances	65	(139)	86	(222)	46	(96)	19	40	–21
Direct non-medical costs									
Patient and family costs									
Travel	131	(229)	105	(150)	101	(100)	30	4	26
Domestic help	1,297	(4,064)	1,147	(1,936)	840	(1,490)	457	307	150
Opportunity costs†	1,553	(1,965)	1,925	(3,251)	1,759	(3,116)	–206	166	–372
Indirect costs									
Productivity losses									
Absenteeism	517	(1,647)	647	(1,979)	1,133	(3,333)	–616	–486	–130
Presenteeism	300	(740)	320	(774)	555	(1,360)	–255	–235	–20
Total direct costs	5,829	(7,129)	5,525	(4,959)	5,220	(5,133)	611	306	305
Total indirect costs	817	(1,978)	966	(2,283)	1,688	(3,735)	–871	–721	–150
Total societal costs	6,945	(7,327)	6,560	(5,549)	6,908	(6,279)	39	–346	385

CG, waitlist control group.
*E.g. physiotherapist, occupational therapist.
†E.g. for waiting time before treatment.

Table 4 Results of the main and sensitivity analyses (based on 5,000 bootstrap simulations)

	Incremental costs, € (95% CI)	Incremental effects (95% CI)	Mean ICER/ICUR (95% CI)	Distribution over the incremental cost-effectiveness plane			
				NE	NW	SE	SW
Analysis ACTonPain$_{guided}$ vs CG							
Cost-effectiveness analysis (treatment response)	6 (–916 to 953)	0.14 (0.08 to 0.2)	45 (–6,671 to 8,260)	50%	–	50%	–
Cost-utility analysis (QALYs based on AQoL-8D)	6 (–916 to 953)	0.01 (0.005 to 0.015)	604 (–92,924 to 114,325)	50%	–	50%	–
Sensitivity analysis (QALYs based on EQ5D-3L)	6 (–916 to 953)	0.014 (0.004 to 0.024)	438 (–69,407 to 122,314)	50%	–	50%	–
Analysis ACTonPain$_{unguided}$ vs CG							
Cost-effectiveness analysis (treatment response)	–352 (–1,968 to 1,272)	0.12 (0.006 to 0.232)	ACTonPain$_{unguided}$ dominates CG	32%	1%	66%	1%
Cost-utility analysis (QALYs based on AQoL-8D)	–352 (–1,968 to 1,272)	0.013 (0.002 to 0.024)	ACTonPain$_{unguided}$ dominates CG	32%	1%	66%	1%
Sensitivity analysis (QALYs based on EQ5D-3L)	–352 (–1,968 to 1,272)	0.017 (–0.005 to 0.04)	ACTonPain$_{unguided}$ dominates CG	30%	4%	64%	3%
Analysis ACTonPain$_{guided}$ vs ACTonPain$_{unguided}$							
Cost-effectiveness analysis (treatment response)	388 (–1,416 to 2,185)	0.164 (0.034 to 0.29)	2,374 (–11,097 to 25,276)	65%	–	35%	–
Cost-utility analysis (QALYs based on AQoL-8D)	388 (–1,416 to 2,185)	0.008 (–0.003 to 0.019)	45,993*	60%	5%	33%	2%
Sensitivity analysis (QALYs based on EQ5D-3L)	388 (–1,416 to 2,158)	0.01 (–0.01 to 0.031)	37,327*	53%	12%	31%	4%

CG, waitlist control group; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; MPI, Pain Interference Scale of the Multidimensional Pain Inventory; NE, northeast quadrant; NW, northwest quadrant; PGIC, Patient Global Impression of Change scale; ; SE, southeast quadrant; SW, southwest quadrant.
*A dependably accurate 95% CI for this distribution cannot be defined because there is no line through the origin that excludes $\alpha/2$ of the distribution.[73]

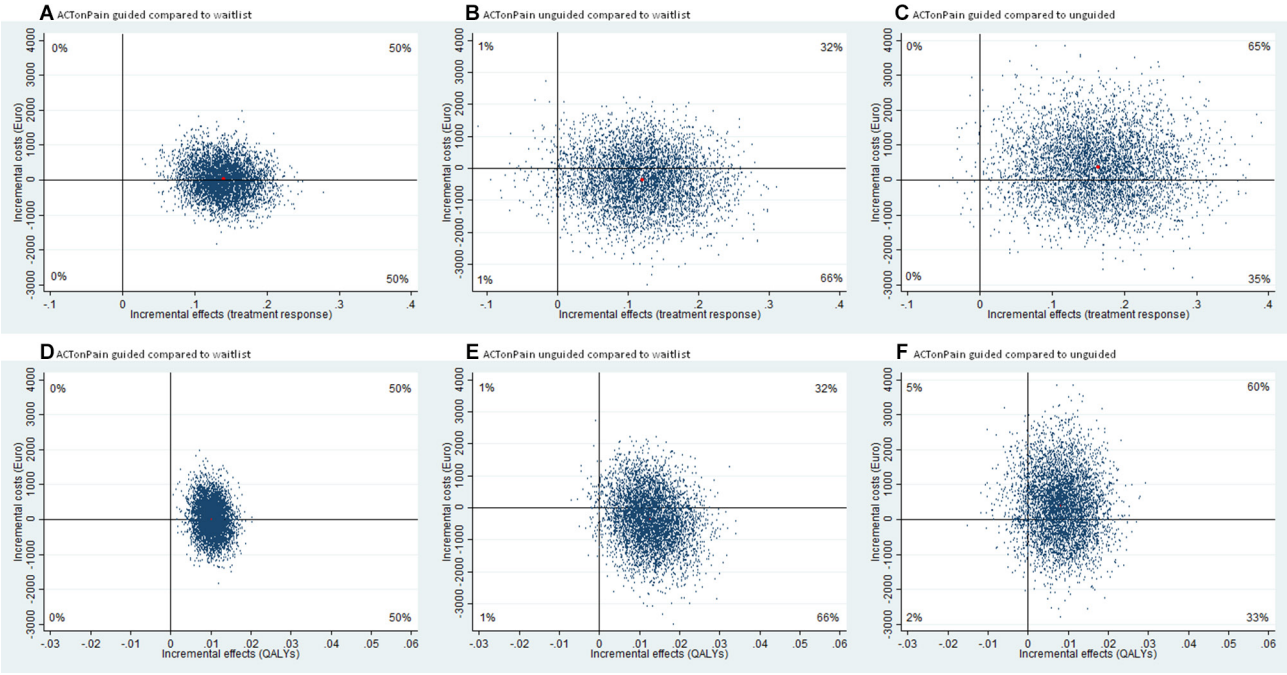

Figure 1 Cost-effectiveness planes of all group comparisons based on 5,000 replicates of the incremental cost-effectiveness and cost-utility ratio using mean differences in costs from a societal perspective and mean incremental effects (treatment response: A–C; QALYs: D–F).

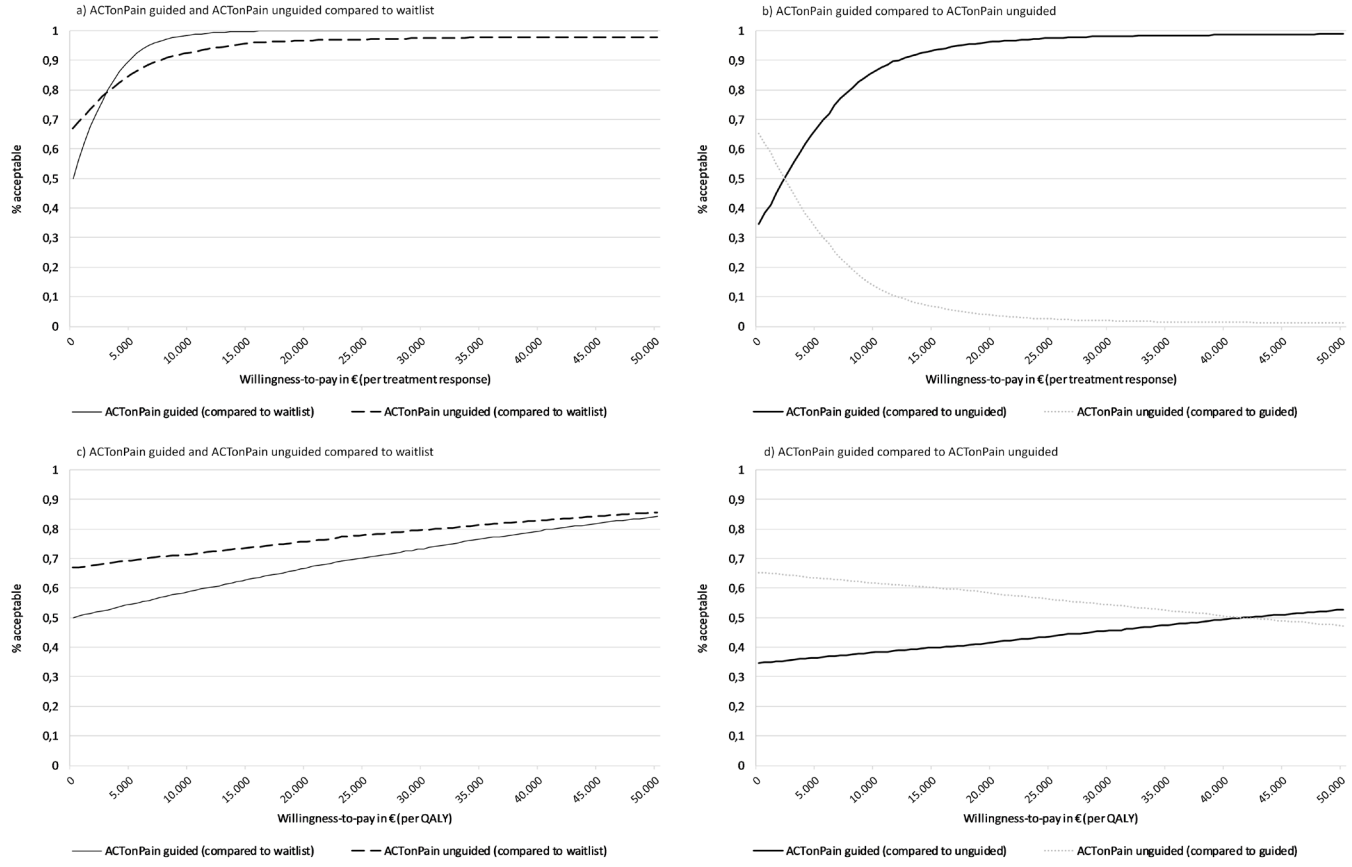

Figure 2 Cost-effectiveness acceptability curves of all group comparisons based on 5,000 replicates of the incremental cost-effectiveness and cost-utility ratio using mean differences in costs from a societal perspective and mean incremental effects (treatment response: A,B; QALYs: C,D). For the comparison of $ACTonPain_{guided}$ vs $ACTonPain_{unguided}$ the inverse function ($ACTonPain_{unguided}$ vs $ACTonPain_{guided}$) is included.

be categorised as a potentially cost-effective treatment (with a probability of being cost-effective of 70%). This threshold might serve as a reference, but it has to be considered that it might differ for the German population.

Here again, uncertainty has to be considered as well as the required WTP for a likelihood of being cost-effective of 95% of €6,490 (treatment response) and €91,000 (QALY gained).

The direct comparison of ACTonPain$_{guided}$ and ACTonPain$_{unguided}$ shows more treatment responders and (slightly) higher QALY gains for the guided version, but at higher costs. In terms of QALYs gained, the guided version only reaches a probability of 35% of being cost-effective at a WTP of €0. Even with rising WTP thresholds, the probability does not increase much.

The results of the sensitivity analyses revealed slightly higher incremental QALY gains by using the EQ5D-3L compared with the AQoL-8D, but overall conclusions are the same as in the main analyses. Estimated EQ-5D-3L utility scores for 1 year ranged from 0.50 to 0.54, what appears rather low compared with national EQ-5D-3L estimates for (back) pain from other countries (e.g. 0.74–0.79[55 56]). Lower estimates in the current study could have occurred due to the socio-demographic properties of this study sample, as participants were predominantly women (84%), reported comorbid medical or mental conditions (57% and 39%, respectively) and the back was the most often reported pain location (34%).[25] Several studies showed that the mentioned characteristics (female sex, musculoskeletal and mental disorders) are associated with lower quality of life scores.[55–57] Furthermore, Burström and colleagues reported that participants with low back pain showed quality of life weights of 0.55,[57] which is comparable to the sample in the current study.

The conclusion that ACTonPain has the potential of being cost-effective is in line with a recent study and a systematic review.[23 58] The guided IMI for chronic pain of Boer and colleagues revealed an ICER of 40 (defined as cost savings of €40) for a one-point improvement in a pain catastrophising scale compared with a face-to-face group intervention.[23] QALYs were not reported. ACTonPain$_{guided}$ reached (slightly) higher ICERs for the clinical outcome pain interference (€45 compared with the CG group and €2,374 compared with the unguided group). However, these values were calculated for treatment response in terms of pain interference and therefore a meaningful change. In a recent systematic review, IMIs for depression that were classified as cost-effective were all guided and showed probabilities of being cost-effective between 28% and 49% at a WTP of €0 for a QALY gained. ACTonPain$_{guided}$ and ACTonPain$_{unguided}$ reached higher probabilities at this WTP level (50% and 67%, respectively). However, it has to be considered that in terms of QALY gain society has to invest quite high sums of money for high probabilities (95%) of being cost-effectiveness. Nevertheless, implementing psychological e-health approaches in pain management programmes might be promising from an economical point of view when compared with the well-established area of depression e-health care.

The higher direct costs over a 6-month period in both intervention groups compared with the CG might be explained by higher or stable healthcare utilisation similar to findings in a previous study on the costs of established depression treatments.[59] However, research indicates that indirect rather than direct costs represent the majority of overall costs,[60 61] where ACTonPain seemingly has its core advantage. Mean indirect costs over the 6-month period were almost half as high in the intervention groups compared with the CG, regarding both absenteeism and presenteeism.

Next to the questions of whether ACTonPain is cost-effective compared with the CG and whether it should rather be provided guided or unguided, a further question would be of interest: How does ACTonPain perform compared with established medical, psychological, physiotherapeutical and surgical treatments that result in high direct costs?[62–65] Surprisingly little is known about the cost-effectiveness of these established pain treatments. In two reviews, it was highlighted that interdisciplinary pain rehabilitation programmes are more cost-effective or produce lower costs than interventions such as surgery and conservative care.[66 67] For individuals with low back pain, it was concluded that interdisciplinary rehabilitation, exercise, acupuncture, spinal manipulation and CBT are potentially cost effective.[68] A further systematic review focused on economic evaluations of third-wave CBT therapies (including ACT). ICURs ranged from negative ICURs indicating dominance over the control group (National Health Service perspective) to €56,637 (societal perspective) per QALY gained.[13] When compared with the CG the ICURs based on the AQoL-8D in this study were €604 and negative (indicating dominance of the unguided intervention over the CG) per QALY gained. Thus, it can be concluded that ACTonPain, as an example of an innovative IMI for the treatment of chronic pain, is effective[25] and could be a cost-effective intervention. A comparison across treatment approaches for chronic pain, however, cannot be provided. Evidence for the cost-effectiveness of established pain treatments is rather weak and the comparability of results across studies is limited due to very heterogeneous methods across trials.[69]

Limitations

First, when interpreting the results, it has to be considered that the study was not powered to statistically test health economic differences. Second, the costs and effects were evaluated over 6 months. Therefore, no conclusions regarding the long-term cost-effectiveness can be drawn. Furthermore, costs between randomisation and 3 months after randomisation were calculated with the AUC method. This is just an estimate and not a representation of the actual costs incurred during this period. Fourth, costs were assessed via self-report. However, the questionnaire used in this study is a valid instrument for recall periods up to 3 months.[70] Finally, the usage of multiple imputation techniques is frequently recommended (e.g. predictive

mean matching).[71] We used a single imputation approach as it was done in the main (effectiveness) analysis,[25] which might not truly reflect missing data uncertainty. However, the comparison with cost and QALY outcomes of complete case analysis revealed only small differences, indicating that the risk of implausible values due to single imputation in this evaluation is low.[72]

Implications and future research

For patients with chronic pain, IMIs might become an important alternative to established interventions. IMIs can expand treatment options for people, whose physical impairment or location makes access to relevant care difficult.[19] Findings from this health economic evaluation study show that depending on the society's willingness-to-pay, both versions of ACTonPain have the potential of being cost-effective, with the unguided version even leading to lower costs (compared with the CG). However, uncertainty has to be taken into account. The decision whether to choose the guided or the unguided version is a public health issue and strongly depends on whether to mainly focus on patient's health or society's resources. Under health economic aspects, ACTonPain$_{unguided}$ should be the preferred intervention, especially when considering the intention of treatment implementation into the healthcare system and scaling up mental healthcare for pain patients.

Future research should especially focus on studies with high methodological quality that are powered to statistically test health economic differences. Furthermore, long-term follow-up studies and evaluation of the (comparative) cost-effectiveness of different guidance formats of IMIs, particularly of ACTonPain, and established pain treatments are needed. Moreover, future studies should examine ACTonPain as integrated part of multi-component pain programmes and aim to dismantle the intervention components that are effective and cost-effective in those complex approaches.

Author affiliations
[1]Department of Sports and Sport Science, Sport Psychology, University of Freiburg, Freiburg, Germany
[2]Department of Rehabilitation Psychology and Psychotherapy, Institute of Psychology, University of Freiburg, Freiburg, Germany
[3]Department of Clinical Psychology and Psychotherapy, University of Erlangen-Nuremberg, Erlangen, Germany
[4]Department of Psychiatry, Psychotherapy and Psychosomatics, University of Aachen, Aachen, Germany
[5]Department of Clinical Psychology and Psychotherapy, University of Ulm, Ulm, Germany

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Patient consent for publication Not required.

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