Cost-effectiveness of upper extremity dry needling in the rehabilitation of patients with stroke

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ABSTRACT

Introduction: Dry needling has shown to be effective for the treatment of upper extremity hypertonia in patients with stroke. **Purpose:** to evaluate cost-effectiveness of dry needling in stroke patients. **Methods:** A cost-effectiveness analysis was performed in a research study conducted at a Spanish public hospital where patients were classified into two groups with or without dry needling. Hypertonia was measured using the Modified Modified Ashworth Scale (MMAS), and quality of life was assessed using the EuroQoL 5-dimension questionnaire. Data regarding the effects and costs of physiotherapy were presented by calculating the mean and 95% confidence interval. The health outcomes were evaluated considering the rate of responders to the treatment based on the MMAS. Spanish preference weights were used to estimate quality-adjusted life years. Incremental cost-effectiveness (ICER) and cost-utility ratio (ICUR) were calculated to determine the economic value of dry needling. **Results:** 80 patients with stroke in the sub-acute stage of recovery were selected to participate in this study. Based on the rate of responders, the ICER of the dry needling group was very low. Despite the sensitivity analysis performed, the results of the ICUR were not encouraging. **Discussion:** Cost-effectiveness with responder rate results are favourable for the dry needling group and are confirmed with the sensitivity analysis by levels of care. Additionally, our findings reveal that four weeks of treatment could be more cost-effective compared to eight weeks. Dry needling treatment of the upper extremity is cost-effective based on the rate of responders measured using the MMAS scale.

KEYWORDS:

dry needling, cost-effectiveness, cost-utility, stroke, upper extremity, EQ-5D-5L

INTRODUCTION

Stroke is the second and fourth cause of death in Spain and Europe, respectively, and also the first cause of acquired disability among adults in Spain [1]. Patients who survive this disease experience a number of complications and sequelae, entailing a major social and health expenditure in both the short and long term [2]. Upper extremity impairment is most common after stroke, with patients experiencing pain, hypertonia, weakness and associated reactions. These complications interfere with motor recovery [3], causing a detrimental effect on quality of life (QOL) and independence in activities of daily living (ADL) [4]. Almost 20% of patients have some degree of hypertonia in the affected extremity in the short and long term [5], most frequently affecting the flexor muscles, with reduced movement fluidity and an imbalance between the flexor and extensor muscle groups, in favour of the former [6].

Different pharmacological alternatives exist for the treatment of hypertonia, such as Botulinum toxin A (BTX-A) infiltrations. Recently, non-pharmacological approaches have been used effectively, such as dry needling (DN), which has shown to be effective at decreasing hypertonia, improving active and passive range of motion in the upper extremity [7] and managing pain [8]. Thus, DN is considered a safe technique when applied by an experienced physiotherapist [9]. Compared to BTX-A injections, the severity of adverse effects are much lower for DN [10]. The main difference between these two treatments is that DN causes a mechanical denervation of the dysfunctional endplates whilst BTX-A injections provoke a chemical denervation of the same [11].

However, although a number of cost-effectiveness studies exist on the application of BTX-A [12,13] in stroke patients, in the case of DN there is a lack of reporting, where studies have only been found in the case of pain treatment for musculoskeletal patients [14]. For this reason, our aim was to analyse the cost-effectiveness of DN in the treatment of hypertonia in patients with stroke, based on a cost-utility analysis in euros per years of quality-adjusted life (QALY) and cost-effectiveness, using response to treatment based on the modified modified Ashworth scale (MMAS) as the main outcome variable.

METHODS

Study design

An economic evaluation was performed following a previous study conducted at Guadarrama Hospital (Madrid, Spain) between 2016 and 2018[15]. It was a single-centre, observational, prospective, single cohort study with a before-after design to compare the effectiveness of the DN technique for the improvement of the motor function

and hypertonia of the affected extremity. All the patients signed an informed consent document before participating. The study was approved by the Clinical Research Ethics Committee of Puerta de Hierro Majadahonda Hospital (act nº 14.17, dated 24 July 2017) and was registered at ClinicalTrials.org (ref. NCT03462693).

Participants

Patients were included in the study if they fulfilled the following criteria: (1) 18 years old or older; (2) diagnosis of ischemic or hemorrhagic stroke in the subacute phase (1 to 3 months); (3) ability to read, understand and sign the informed consent prior to commencing the study; and (4) grade 1 to 3 hypertonia in the affected upper extremity muscles measured using the MMAS. The exclusion criteria were as follows: (1) grade 0 (flaccidity) or 4 (rigidity) hypertonia according to the MMAS; (2) receipt of BTX-A treatment in the previous two months; (3) cognitive or severe language impairment; (4) insurmountable needle phobia; or (5) any medical contraindication to the application of DN. A propensity score analysis was used to pair the patients in each group according to baseline demographic and clinical variables in order to have a quasi-randomised design, obtaining two comparable groups without significant differences at baseline.

Intervention conditions

Patients received standard physiotherapy treatment according to the standardized work plans used in daily clinical practice at Guadarrama Hospital. The treatment protocol consisted of a multimodal approach for the affected upper extremity, focusing on reducing hypertonia, passive positioning of the upper extremity and repetitive task training exercises [16], lasting 45 minutes, five days a week. The eligible patients included in the study were treated by their usual physiotherapist and were classified into two groups depending on whether they were receiving DN in their session. The DN intervention was applied following specific diagnostic and application criteria described for neurological patients (DNHS®)[17]. DNHS treatment was included in six of the standard treatment sessions (weeks 1, 2, 3, 4, 6 and 8) according to the normalized protocol used at Guadarrama Hospital for the application of DN. The control group consisted of patients who received their normal rehabilitation program with neither DN nor a placebo during the same eight weeks, five days a week.

Main measures

The two variables used for the main study were the MMAS and the values of the EuroQol-5D questionnaire (EQ-5D-5L). The EQ5D is one of the most recognized and employed patient reporting outcomes (PRO) questionnaires,

including five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five levels of severity, which makes it even more robust than previous versions [18]. Furthermore, the EQ5D correlates well with functional recovery and its use has been validated in patients with stroke [19]. To obtain the QOL value based on the EQ5D questionnaire data, the "EQ-5D-5L Index Value Crosswalk" tool was used with Spanish preference weights. Using the study timing it was possible to obtain QALYs, which represent the preferred measure of health outcome for use in technology appraisals [20]. The EQ-5D-5l survey was completed at the beginning of the study and repeated at four and at eight weeks.

Use of the EQ5D, together with other more specific instruments such as the rate of responders, is recommended in order to increase the discriminative power and/or sensitivity to change [21]. For this purpose, hypertonia was measured using the MMAS to evaluate response to treatment. The MMAS allows us to assess whether a patient has normal muscle tone or presents some type of mild, moderate, intense or extreme hypertonia. The MMAS is an ordinal scale that scores resistance to passive movement ranging from 0 (no increase in muscle tone) to 4 (rigidity in flexion or extension) via passive stretching of the affected muscle group. This scale shows good intraobserver ($\kappa w=0.84$)[22] and interobserver ($\kappa w=0.81-0.89$) [23,24] reliability. In this case, the resistance to shoulder abduction, elbow extension, elbow flexion, forearm supination, wrist extension and finger extension was measured. The MMAS measurements were made before and after the six sessions of DNHS®.

Costs

The economic evaluation was made from the perspective of a hospital, clinic or health centre; thus, direct health care costs were calculated, such as the material used to perform the DN (sterile gauze, disinfectant, needles), the cost of the physiotherapy sessions and the level of care. The costs were assessed based on the number of needled muscles and assuming proper use of the skin disinfection material. Direct health care costs were estimated by calculating the average cost of a physiotherapy session for upper extremity treatment of patients with stroke in five representative regions of Spain (Aragón, Castilla y León, Madrid, Basque Country and Catalonia). In the case of the cost of the physiotherapy sessions, DN was performed without altering the number of or duration of the sessions. Because of this reason, there were no differences between groups for the cost of the physiotherapy sessions. The average costs per patient stay were assessed according to levels of care based on data from the year 2016 provided by Guadarrama Hospital.

Outcomes

The rate of responders and health-related QOL were measured at baseline, and at four and eight weeks. The rate of responders to treatment was calculated using the MMAS values. A patient was considered to have responded to treatment if an improvement by one point or more on the scale was detected between the first measurement and the last. The data were transformed to obtain the percentage of patients responding to treatment in both branches of the trial at four and at eight weeks [12]. With the same timeline, EQ-5D-5L responses were converted into utility score. Then QALY were estimated for each subject using area under the curve analysis.

To calculate the economic analysis based on the QALYs, the rate of treatment responders and estimated costs, the cost per responder and the cost per QALY were calculated for each group. Due to the complexity of the MMAS scale, the costs per responder were assessed for each movement: shoulder abduction, elbow extension, elbow flexion, forearm supination, wrist extension and finger extension. Subsequently, the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) were calculated. This ratio represents the cost per additional QALY gained for ICUR and per additional percentage of responders for ICER over the treatment period compared to the control group. It was calculated by dividing the incremental cost by the incremental QALY or percentage of responder patients.

Statistical analysis

The distribution of the data was verified by the Kolmogorov-Smirnov normality test and a factorial analysis of variance (ANOVA) was performed to evaluate the differences**.** To compare costs between groups, the direct cost per responder was calculated together with the cost per QALY. As the care levels were the most important costs included in the study, the economic study was segmented by these levels.

To analyse the uncertainty of QALY, the probabilistic bootstrapping method was applied. To summarize uncertainty, this study considered the proportion of bootstrap replications that fell below and to the right of the line of the cost-effectiveness threshold. This was represented by the cost-utility acceptability curve (CUAC) [25]. The cost-effectiveness threshold, although not established, was between 22,000 and 25,000 € in Spain [26].

RESULTS

A total of 80 patients aged 73.2 ± 13.3 years were included in the final economic analysis. There were no differences between groups in characteristics such as age, body mass index (BMI), time since stroke and other concomitant illnesses at baseline (Table 1).

Table 1. Demographic characteristics of participants and other baseline characteristics

		Control group n=40	Intervention group (DNHS®) n=40	P Value
Gender (male)		20 (50%)	20 (50%)	N/A
Age (years)		73.8 (±12.7)	72.6 (±13.8)	0.995
Body mass index (kg/m^2)		25.6 (±3.8)	24.9 (±4.1)	0.758
Time since stroke (days)		32.4 (±17.8)	39.7 (±18.8)	0.908
Type of stroke	Haemorrhagic	17 (43%)	19 (48%)	0.434
	Ischaemic	23 (57%)	21 (52%)	
Side of body	Right	16 (40%)	17 (43%)	1.000
	Left	24 (60%)	23 (57%)	
Smoker	No	32 (80%)	30 (75%)	0.789
	Yes	8 (20%)	10 (25%)	
Diabetes mellitus	No	27 (68%)	30 (75%)	0.621
	Yes	13 (32%)	10 (25%)	
Hypertension	No	16 (40%)	13 (32%)	0.642
	Yes	24 (60%)	27 (68%)	
Heart disease	No	25 (62%)	24 (60%)	1.000
	Yes	15 (38%)	16 (40%)	
Level of care Level 1 Level 2 Level 3 Level 4		 0 24 (60%) 11 (28%) 5 (12%)	 1 (3%) 17 (42%) 12 (30%) 10 (25%)	0.231**
Baseline		0.250 ± 0.386	0.050 ± 0.437	0.442

Quality of life (EQ-5D-5L, 0-1)	4 weeks		0.323 ± 0.392	0.422 ± 0.369	1.000
		Difference from baseline	(+0.073, p=1.000)	(+0.372, p=0.000)*	
	8 weeks		0.321 ±0.372	0.338 ±0.421	1.000
		Difference from baseline	(+0.071, p=1.000)	(+0.288, p=0.001)*	

*All values are means (± standard deviation) or number of patients (%). Difference in means is significant if p<0.05. ** Excluding level 1, which only had one case.

Costs

The calculations used in this study to determine the costs of treatments are displayed in Table 2. The approximate average cost of a physiotherapy treatment session provided in the Spanish public health system for a stroke patient is approximately 15.92 € (1.60+14.32). The differences between groups were due to the cost of the material used for DN: 6.40 € for four weeks and four sessions with DNHS and 9.60 € for eight weeks and six sessions. The cost of physiotherapy sessions was determined based on the official bulletins of each of the five representative autonomous communities, ranging from 7.75 € per session in Castilla y León to 20.08 € in Aragón. There were no differences between groups in costs according to levels of neurological patient care in this study.

Table 2. Costs

		Unitary cost (taxes not included)	4 weeks		8 weeks	
			Control Group	DNHS Group	Control Group	DNHS Group
Dry needling (material per session and muscle)		1.60 € Min. 0.64€. Max. 2.56€	-	6.40 €	-	9.60 €
Physiotherapy (session)		14.32 € ±4.39€	286.40 €	286.40 €	572.80 €	572.80 €
Total treatment costs per protocol			286.40 €	292.80	572.80 €	582.40 €
Levels of care (average cost per day of neurological patients by levels of care, year 2016,	Level 1	187.61 €	-	5,545.88 €	-	11,088.56 €
	Level 2	253.28 €	7,378.24 €	7,384.64 €	14,756.48 €	14,766.08 €
	Level 3	1,065.62 €	30,123.76 €	30,130.16 €	60,247.52 €	60,257.12 €
	Level 4	1,016.67 €	28,753.16 €	28,759.56 €	57,506.32 €	57,515.92 €

Guadarrama Hospital)						
Mean cost			16,022.59 € (± 1,737.77)	19,503.11 € (± 1,802.26)	32,253.77 € (± 3,381.76)	39,036.23 € (± 3,651.51)

*(± standard deviation)

Quality of life

No significant differences between groups were found in the QOL of the patients at baseline. QOL improved during the eight-week duration of the study in both groups; however, significant differences were only found in the DNHS treatment group at 4 and 8 weeks (Table 1).

Regarding the utility values estimated using bootstrap methods, a significant difference was found in favour of the Control group at four weeks, however at eight weeks there was no significant difference.

Bootstrapped cost-utility pairs were illustrated by drafting a cost-utility plane and acceptability curves (Figure 1). After resampling, most of the results appeared above the threshold: only 7.5% of the cases were cost-effective at four weeks and 8% at eight weeks. This indicates that there was no improvement in utility or cost using DNHS.

We observed a large impact on the costs according to level of care. Thus, it was necessary to perform a sensitivity analysis by assessing each care level separately (Figure 2). Due to a lack of patients at level 1, only levels 2, 3 and 4 were assessed. In this case, patients were separated according to their level of care, and the willingness to pay was lower. At four weeks, level 2 and 3 patients could achieve 50% of cost-effective results.

Treatment responder rate according to the MMAS scale

The administration of the MMAS scale involves the measurement of six muscle movements. An improvement of 1 point on this scale in one of the movements is considered a response to treatment. The results of this scale were clearly favourable in the DNHS treatment group presenting significant improvements in elbow flexion, forearm supination and wrist extension at four and eight weeks. In the DNHS treatment group there was an average of 92% of patients who responded favourably at four weeks versus 18% in the Control group, and 70% versus 17% at eight weeks. From an economic perspective, in all cases, the cost per responder was most inexpensive for the group receiving DNHS (Table 3).

Table 3. Rate of responders to treatment and cost per responder

	4 weeks								8 weeks							
	Control			DNHS®					Control			DNHS®				
	n	% responder [95%CI]	€/responder	n	% responder [95%CI]	€/responder	McNemar test	ICER	n	% responder [95%CI]	€/responder	n	% responder [95%CI]	€/responder	McNemar test	ICER
Shoulder adduction	16	13% [±16.20%]	128,180.7 €	4	100% [-]	19,503.11 €	0.250	3,977.74 €	16	13% [±45.83%]	258,030.16 €	4	75% [±42.43%]	52,048.31 €	0.250	10,851.94 €
Elbow flexion	31	13% [±11.80%]	124,175.07 €	30	90% [±10.74%]	21,670.12 €	0.000*	4,514.48 €	31	16% [±32.24%]	199,973.37 €	30	47% [±17.85%]	83,649.06 €	0.035*	22,210.17 €
Elbow extension	16	50% [±24.50%]	32,045.18 €	11	91% [±16.99%]	21,453.42 €	1	8,507.94 €	16	44% [±36.75%]	73,722.90 €	11	91% [±16.99%]	42,939.85 €	0.500	14,382.08 €
Forearm supination	37	5% [±7.29%]	296,417.92 €	16	94% [±11.86%]	20,803.32 €	0.000*	3,939.71 €	37	5% [±31.34%]	596,694.75 €	16	69% [±22.71%]	56,779.97 €	0.006*	10,707.24 €
Wrist extension	35	14% [±11.59%]	112,158.13€	18	94% [±10.58%]	20,650.35 €	0.001*	4,342.03 €	35	14% [±30.67%]	225,776.39 €	18	72% [±20.69%]	54,050.16 €	0.039*	11,706.71 €
Finger extension	18	11% [±14.52%]	144,203.31€	11	82% [±22.79%]	23,837.13 €	0.500	4,922.45 €	18	11% [±43.55%]	290,283.93 €	11	64% [±28.43%]	61,342.65 €	0.500	12,912.76 €
MEANS		18%	139,530.05 €		92%	21,319.58 €		5,034.06 €		17%	274,080.25 €		70%	58,468.33 €		13,795.15 €

* the difference in means is significant if p-value<0.05

To verify whether these results varied according to the level of care, the analysis was repeated in a segmented manner. According to this method, the cost per responder of the control group exceeded that of DNHS into 69,492.02 € in level 2 and 73,473.20 € in level 4 at 4 weeks and exceeded 100,000 € in the others. The differences were significantly in favour of the group receiving DNHS.

The distribution of the data in the cost-effectiveness plane revealed that all the data, when segmented by levels of care, were well below the 25,000 € threshold considered for cost per QALY.

DISCUSSION

This study has evaluated the effectiveness of DN treatment in upper extremity rehabilitation in patients in the sub-acute phase of stroke, based on the improvement of hypertonia and quality of life and considering the cost of this technique. The baseline characteristics of the patients were very similar for the intervention and control arms, based on a propensity analysis and therefore the difference of costs between groups are not related to other diseases or baseline characteristics. However, we observed certain differences in the distribution of patients according to the levels of care. Therefore, we decided to carry out the sensitivity analysis by level of care.

Regarding hypertonia outcomes, measured with the MMAS, in all cases, the responder rate was favourable to the DNHS® group. Although a direct comparison cannot be made with other studies, the results obtained in our study are similar to the study carried out by Rychlik et al. [12], who evaluated incobotulinumtoxinA infiltration against the standard treatment, consisting of the combination of physiotherapy with oral medication. Comparing this data with the present study, the responder rate in shoulder abduction was 100% at four weeks and 75% at eight weeks for DNHS® vs 62.9% at one year for BTX A; for elbow flexion it was 90% at four weeks, 47% at eight weeks for DNHS® vs 83.8% at one year for BTX A; for wrist extension it was 94% at four weeks and 72% at eight weeks for DNHS® vs 86.2% at one year for BTX A. Although the timelines were not comparable, the data is very similar in both studies.

According to our findings, no significant differences were found for the EQ5D scores between groups, which is similar to the results found by the BoTULS study, performed on the upper extremity of stroke patients [13], and which showed that treatment with BTX-A did not result in any important improvements in stroke-related quality of life. Unlike this study, the DNHS treatment group displayed significant improvements in the quality of life at four weeks compared to the baseline value 0.422 ±0.369 (+0.372, $p<0.05$).

In terms of costs, the main difference we found in the average total costs (*Table* 2 *Costs*) was mainly due to the cost of the care levels of patients with stroke, which is the greatest burden because of the complexity of the disease. Levels 3 and 4 represent the largest economic burden. The cost per session of physiotherapy treatment is not

standardized in Spain and this may vary depending on each Autonomous Community and each centre (±4.39€). Because of this, the assessment of the cost of the physiotherapy session and the material used is slightly higher than that described by Arias-Buria et al. 2018 [14], who reported an estimated cost of physiotherapy sessions of 14.32€ (±4.39€) vs. 10.03€ (±5.9) and a material cost for DN of 0.64€ vs. 0.35€.

The cost per QALY of each group was similar at four weeks of treatment although this varied at eight weeks of treatment, with better results in the control group, due to costs related with levels of care. As observed in Table 1, there was one patient in care level 1 in the DNHS treatment group, however no patients for this care level in the control group. In addition, the distribution by levels can influence the average costs, despite the lack of significant differences, therefore a sensitivity analysis is necessary. The cost-utility analysis with the quality of life values of the EQ5D and care levels costs were not very promising. According to bootstrap sensitivity analysis, DNHS® appears to be cost-effective in less than 10% of cases. Care levels represent the greatest economic burden and therefore it was necessary to carry out a sensitivity analysis according to levels of care to determine in which cases this is cost-effective. Our study revealed that four weeks of DNHS® treatment for patients in care levels 2 and 3 could have greater odds of being cost-effective than physiotherapy alone, which is in line with results obtained in other studies, such as a study using DN to treat subacromial pain syndrome [14], which reported that the inclusion of the DN technique in conventional treatment has a better cost-effectiveness ratio than conventional exercise for one year, based on the same quality of life questionnaire EQ5D-5L.

These results lead us to believe that the use of EQ5D to evaluate this type of treatment in a stroke population is not ideal. In this case, we consider that the EQ5D may not be as sensitive to quality of life variations in patients whose quality of life is rather poor, or when the variations in the quality of life with treatment are limited [27]. The use of the 'responder rate' variable appears to be more appropriate than the EQ5D to detect improvements with DN treatment in patients with stroke.

Cost-effectiveness with responder rate results were positive in all cases for DNHS® and were confirmed with the sensitivity analysis by levels of care. Besides, our findings indicate that four weeks of treatment could be more profitable than treatments lasting eight weeks considering the cost per responder: the mean difference between cost per responder at four weeks is 37,148.75€ cheaper than at eight weeks. Therefore, it would be necessary to analyse whether it is clinically necessary to extend treatment to eight weeks. It would also be interesting to know how this situation evolves up to one year after treatment and be able to compare this with other treatments such as BTX-A in the BoTULS study [13].

The main limitation of this study concerns the measurement of the quality of life in patients with stroke. The use of the EQ5D scale did not allow us to verify the variations in the quality of life of these patients; furthermore, this scale does not appear to be very sensitive to these variations of hypertonia. In other cases, certain studies indicate that although the EQ5D, may be very useful for a variety of diseases, in line with other scales measuring quality of life (Sickness Impact Profile SIP, SF-36, Well Being Scale or Nottingham health profile), it may be less sensitive for examining the specific effects of certain diseases, such as stroke, for evaluating quality of life and the impact of treatments [28]. Additionally, we encountered several difficulties when comparing our data with other studies because of differences affecting the study duration or the measurement times for gathering QoL data.

In future studies, a direct comparison between BTX-A and DNHS® is necessary, as the effectiveness of DNHS® and BTX A infiltration was very similar in the rate of responders [12] and in the quality of life according to the EQ5D [13]. In addition, the comparison of our results with the data obtained in the BoTULS study enables us to assume that the utility values with the EQ5D would be similar. Regarding costs, as reported in the study by Andrés-Nogales et al. [29], the annual cost of the toxin vials for adult patients with spasticity in the upper extremity can range between 529.87€ to 1180.72€. Because of this, and considering the cost of physiotherapy treatment, it is reasonable to consider that including a specific DN treatment in a standard physiotherapy program may involve a cost saving compared to BTX A infiltration. However, our study doesn't allow us to confirm the benefits of DN against BTX-A and, therefore, further research is needed to confirm and expand on these findings.

In this study, a cost-effectiveness analysis was conducted using two different effectiveness variables: a PRO as the EQ5D for quality of life and another direct variable: hypertonia measured using the MMAS. The effectiveness data calculated in this study are clearly positive to treatment with DNHS® for the upper extremity in patients with sub-acute stroke, according to the rate of responders. However, according to utility values, quality of life did not show statistically significant improvements. Likewise, these results are transferred to the economic analysis.

When the quality of life was assessed with the EQ5D questionnaire, it only appears to be favourable in less than 10% of the cases, which is a finding that we attribute to the low sensitivity of this tool in these cases or to the pathology itself. The findings regarding the rate of responders are clearly more positive in the case of the DNHS® treatment. The low cost of the DNHS® technique and the positive data regarding the rate of responders, based on the MMAS scale, are indicators that DN may be a good alternative for the treatment of the upper extremity in patients with stroke in the sub-acute phase.

DECLARATION OF INTEREST

The DNHS® technique was registered by Pablo Herrero. The other authors of this work declare that there are no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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FIGURE LEGENDS

Figure 1

Bootstrapped cost-utility pairs and acceptability curve. Red line: 25,000 € cost-utility threshold. [A] Four weeks incremental cost-effectiveness plane. [B] Eight weeks incremental cost-effectiveness plane. [C] Cost-utility acceptability curve for four and eight weeks of treatment.

Figure 2

Cost-utility acceptability curve separated by levels of care at 4 and 8 weeks.