

**Botulinum toxin type A for the prevention of headaches in
adults with chronic migraine**

NICE request for additional clarification and results

13 March 2012

Probability sensitivity analyses ICERs

Table 4 of the Allergan document of the 24th of February 2012, includes the probabilistic results applying different utilities to the Botox and placebo arms. Given the Committee's uncertainty regarding the use of different utilities and the impact of this on the ICERs, please provide probabilistic results which incorporate the same utilities to the Botox and placebo arms.

Allergan Response

Correction

In calculating the PSA for the scenario using the same utilities between the two arms, it came to our attention that the continuity correction had been incorrectly applied.

In order to clarify our usage of the continuity correction, we have provided a revised explanation of the method (APPENDIX 1 - technical explanation) . The model has also been provided TO BASECAMP to allow inspection of the PSA methodology. The user can view the beta tree calculations in the Transitions_Botox sheet (rows 80-111), and the Transitions_Placebo sheet (rows 89-130).

The impact on results is minimal, with revised probabilistic sensitivity analysis performed for both the base case (with the different utilities for placebo and Botox), and the scenario with the same utilities on both arms.

In the previously submitted Allergan base case, the deterministic ICER is £14,999. The revised probabilistic mean ICER is £14,959. Full details are shown in Table 1.

Table 1: Probabilistic results - different utilities

Treatment Arm	Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs			
Placebo	£ 2,279	1.14			
Botox	£ 3,479	1.22	£ 1,200	0.08	£ 14,959

The incremental costs and QALYs for 10,000 simulations are plotted in Figure 1.

Treatment with Botox is cost-effective at a threshold of £20,000/QALY on 91% of occasions, and on 99% of occasions at a threshold of £30,000/QALY (Figure 2)

Figure 1: CE scatterplot - different utilities

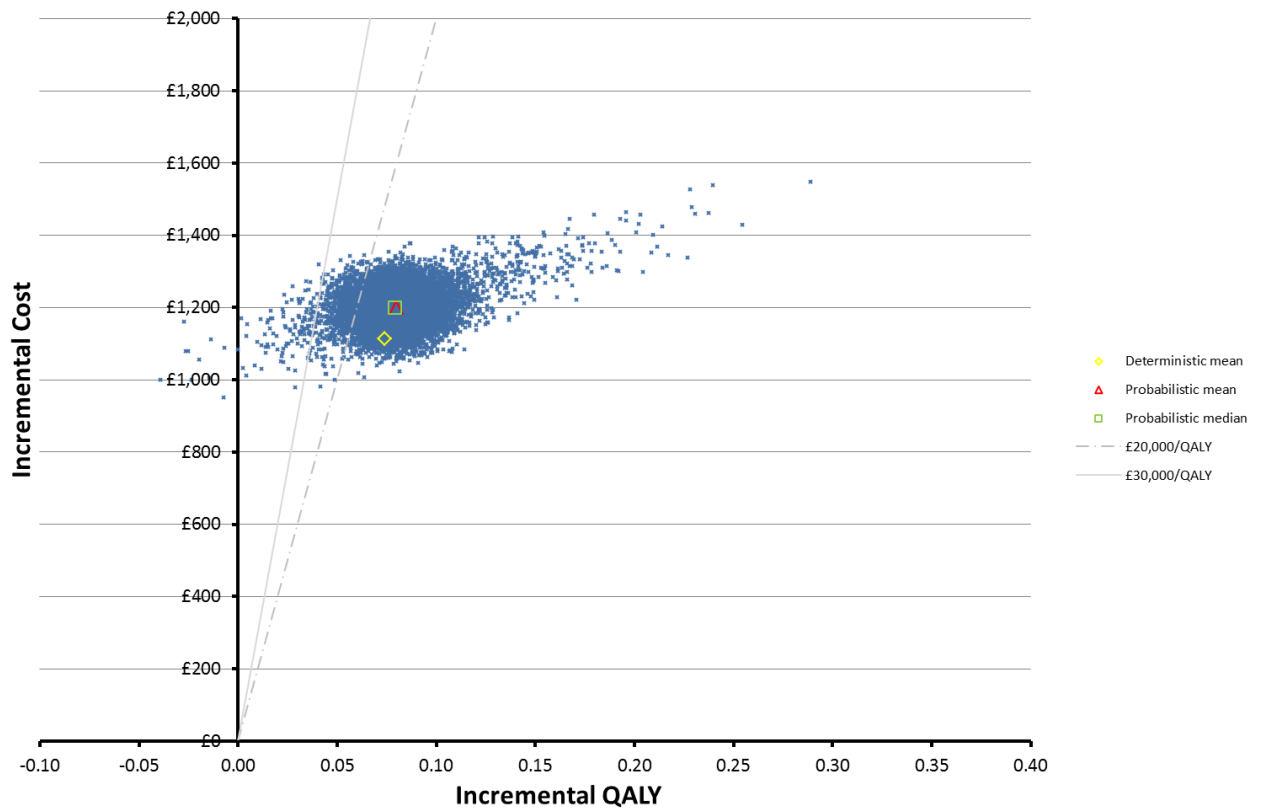
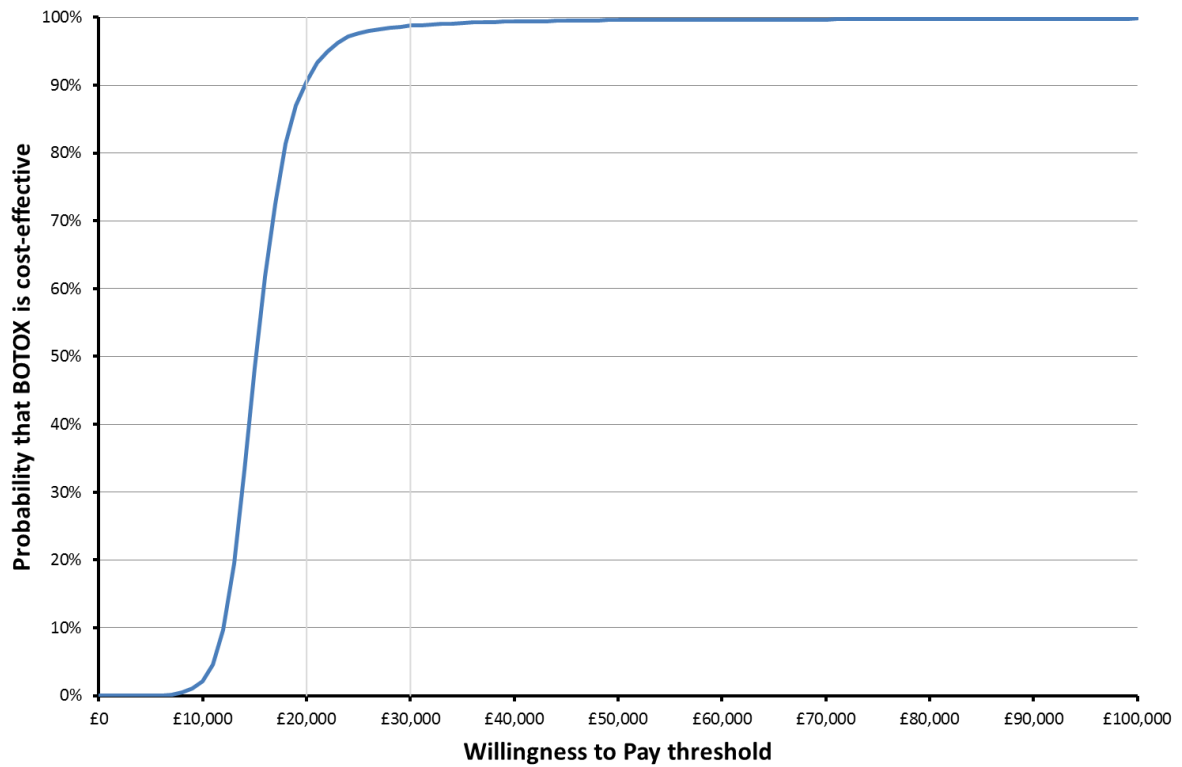


Figure 2: Cost-effectiveness acceptability curve (different utilities)



When the same utilities are applied to both arms, the deterministic ICER is £24,939. The revised probabilistic mean ICER is £25,242. Full details are shown in Table 2.

Table 2: Probabilistic results - same utilities

Treatment Arm	Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs			
Placebo	£ 2,279	1.16			
Botox	£ 3,478	1.21	£ 1,198	0.05	£ 25,242

The incremental costs and QALYs for 10,000 simulations are plotted in Figure 3. Treatment with Botox is cost-effective at a threshold of £20,000/QALY on 20% of occasions, and on 67% of occasions at a threshold of £30,000/QALY (Figure 4.)

Figure 3: CE scatterplot – same utilities

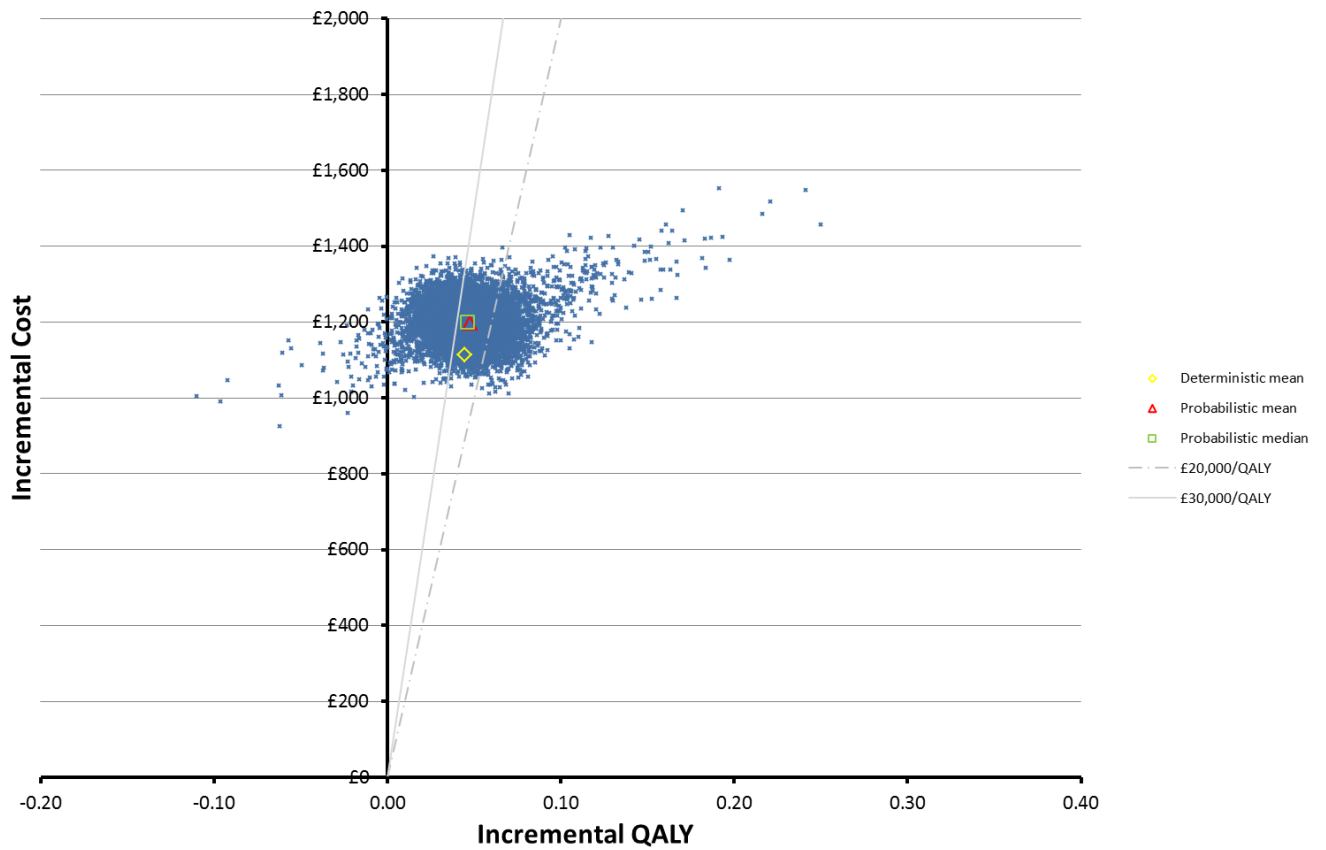
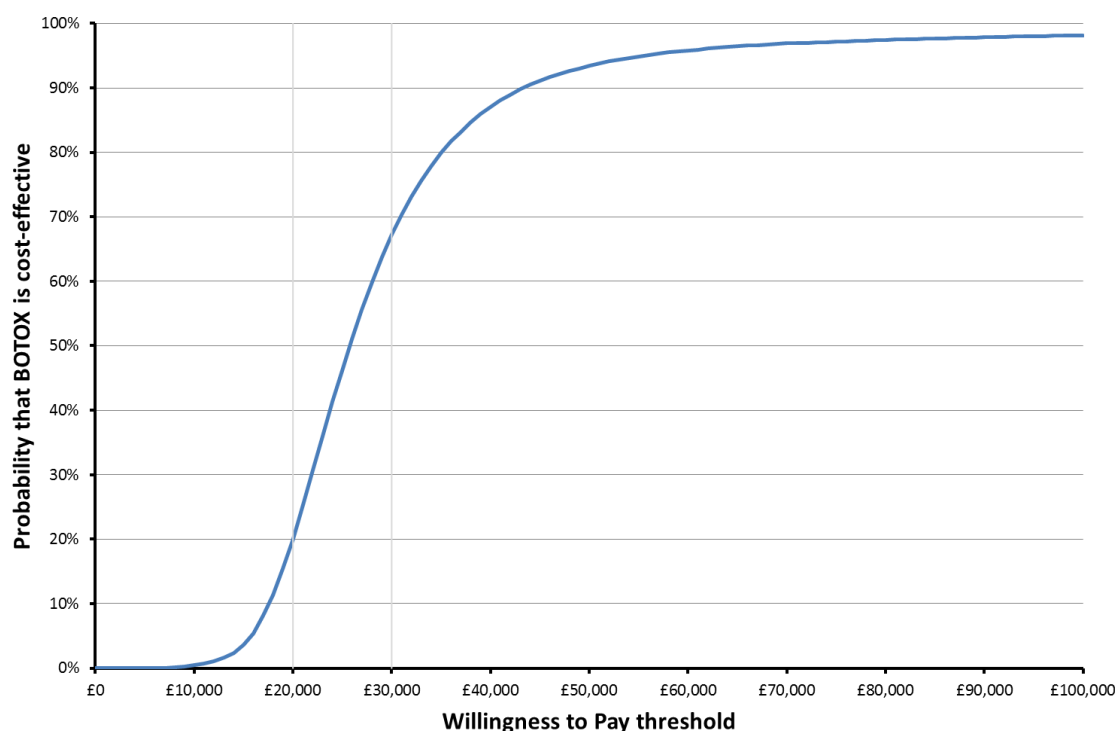


Figure 4: Cost-effectiveness acceptability curve – same utilities



Calculation of utilities

The Allergan document of the 24th of February 2012 provides some details about some of the elements contributing to the calculation of the utilities used in the model. But the document does not provide the level of detail required, and in particular that requested under the 3rd bullet of point 1.5 of the ACD. It would be much appreciated if the following four points could be addressed.

Point 1: Confirmation of approach employed

The ERG's current understanding from section 6.4.3¹ of the Allergan October 2011 submission is that the utility mapping function used within the modelling is the MSQ model of columns 1, 3 and 5 of table 6 of appendix 19 of the Allergan October 2011 submission. The ERG's current understanding is also that this function is applied to the 24 week trial data of the 3+ botox patient population and the 24 week trial data of the 3+ placebo patient population to arrive at the health state utilities used within the modelling.

Please clarify if this interpretation is correct, and if not how the utility modelling differs from it.

Allergan Response

Allergan confirms that the utility mapping model used to produce health-state utility values is that described in columns 1,3, and 5 of table 6 of appendix 19 of the Allergan October 2011 submission. In table 3 of the Utility Correction Correspondence provided by Allergan (December 23, 2011), as well as table 13 of appendix 1 of the Additional Analyses requested following receipt of the Appraisal Consultation Document (February 24th, 2012), this previously described mapping algorithm was applied at week 24 to the 3+ Botox patient population and 3+ placebo patient population.

Point 2: Patient numbers

Tables 14 and 15 of the Allergan document of the 24th of February 2012 report quite different patient numbers. Please provide an account of this. Please also clarify how patients with missing values for some data elements within the utility mapping function have been treated within the utility calculations.

¹ "The final MSQ model used a constant, MSQ domain scores, age, sex, race, employment status, headache medication, pre-existing pain condition, pre-existing vascular condition, pre-existing psychiatric condition and other pre-existing condition to estimate the EQ-5D score which was converted in to a utility using the UK dataset."

Allergan Response

Tables 14 and 15 differ because of missing values. Only patients with complete data for each variable included in the mapping algorithm were able to be included in the calculation of utilities.

Point 3: Treatment of botox as a headache medication within the utility function

The utility mapping function has within it a coefficient for headache medication. Please clarify what parameter value would be applied to this coefficient for:

1. A patient in the placebo arm who was only taking a triptan
2. A patient in the placebo arm who was taking no headache medication
3. A patient in the botox arm who was receiving botox but also taking a triptan
4. A patient in the botox arm who was receiving botox but taking no other headache medication

Allergan Response

The use of any acute or preventive headache medication was considered to be a dichotomous variable with values of 0 or 1. The use of any acute or preventive headache medication other than Botox was assigned a parameter of "1". Table 3. lists the parameters which would be applied to the medication use coefficient in the four scenarios.

Table 3. Parameter for headache medication use in utility mapping

Scenario	Parameter
A patient in the placebo arm who was only taking a triptan	1
A patient in the placebo arm who was taking no headache medication	0
A patient in the Botox arm who was receiving Botox but also taking a triptan	1
A patient in the Botox arm who was receiving Botox but taking no other headache medication	0

Point 4: Detail of the calculation of utilities

It is appreciated that the modelling may have calculated individual patient utilities and then averaged over these rather than have used the mean parameter values across patients to calculate the mean utility value for a given arm and health state.

Despite this, for the sake of simplicity please complete the attached excel workbook² using the mean values of the coefficients and the mean values of the parameter values at 24 weeks for the 3+ PREEMPT patient population for botox and for placebo.

If the workbook contains an error of interpretation by the ERG it would be appreciated if the appropriate corollary of this workbook could be completed. The main principles are that it should have:

1. Six worksheets corresponding to the six health states of the model
2. In each worksheet
 - a. Column A should list the coefficients of the utility mapping function
 - b. Column B should list the mean values of the coefficients of the utility mapping function
 - c. Column C should list the mean values of the parameters for the 3+ group in the botox arm at the relevant time point
 - d. Column D should provide the calculation of how the individual coefficients and mean parameter values for the 3+ group in the botox arm interact
 - e. The foot of column D should provide the appropriate sum of the values calculated as per the above point to arrive at the utility value
 - f. Column E should list the mean values of the parameters for the 3+ group in the placebo arm at the relevant time point
 - g. Column F should provide the calculation of how the individual coefficients and mean parameter values for the 3+ group in the placebo arm interact
 - h. The foot of column F should provide the appropriate sum of the values calculated as per the above point to arrive at the utility value

Allergan Response

The excel workbook has been provided.

² Utilities data for sending to Allergan post ACD.xlsx

APPENDIX 1 - Technical Explanation

The population of patients beginning in a given health state at the start of a cycle are divided into mutually exclusive and exhaustive groups – the health states into which they transition. This can be divided into a number of beta distributions, which is represented with a “beta tree” distribution.

For example, in the placebo arm, between baseline at week 12, the patient transitions from the 15-19 headache days per month health state are shown below:

Table 4: patient transitions from the 15-19 headache days per month health state – baseline to week 12

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	8	25	44	26	6	7	8

HA = headache

The probability of a patient transitioning from 15-19 headache days per month to 0-3 headache days per month can be represented as a beta distribution with alpha = 8 successes, and beta = 116 failures (25+44+26+6+7+8). A random number between 0 and 1 is then used to sample from the beta(8,116) distribution, producing a value p between 0 and 1. The probability that a patient transitions to any of the other states is then 1-p.

The probability of a patient transitioning from 15-19 headache days per month to 4-9 headache days per month can be represented as a beta distribution with 25 successes, and 91 failures (44+26+6+7+8) (excluding transitions to 0-3 headache days per month). A random number is then used to sample from the beta (25,91) distribution, producing a value q between 0 and 1. Since this value q is the probability of transitioning from 15-19 headache days per month to 4-9 headache days per month, given that they do not transition from 15-19 headache days per month to 0-3 headache days per month, the probability of transiting from 15-19 headache days per month to 4-9 headache days per month is $q*(1-p)$.

Similarly, the transition from 15-19 headache days per month to 10-14 headache days per month can be represented with a beta(44,47) distribution (excluding transitions to 0-3 headache days per month and excluding transitions to 4-9 headache days per month), to give a value r. The probability of transiting from 15-19 headache days per month to 10-14 headache days per month is $r*(1-p-q)$.

The probabilistic values for the transition probabilities are therefore:

Table 5: Transition probability calculations

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	p	$q*(1-p)$	$r*(1-p-q)$	$s*(1-p-q-r)$	$t*(1-p-q-r-s)$	$u*(1-p-q-r-s)$	$(1-u)*(1-p-q-r-s)$

HA=Headache

Where p is a random sample from the beta (8, 116) distribution, q is a random sample from the beta (25, 91) distribution, r is a random sample from the beta(44,47) distribution, s is a random sample from the beta (26, 21) distribution, t is a random sample from the beta (6, 15) distribution, u is a random sample from the beta (7, 8) distribution.

Where alpha or beta is below 5, a continuity correction is applied. This continuity correction divides an additional observation equally amongst alpha and beta. For example, in the Botox® arm, between baseline at week 12, the patient transitions from the 15-19 headache days per month health state are shown next:

Table 6: probabilistic patient transitions from the 15-19 headache days per month health state – baseline to week 12

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	15	34	33	16	10	1	6

HA=Headache

These would be represented as shown below:

Table 7: Transition probability calculations

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	p	$q*(1-p)$	$r*(1-p-q)$	$s*(1-p-q-r)$	$t*(1-p-q-r-s)$	$u*(1-p-q-r-s)$	$(1-u)*(1-p-q-r-s)$

HA=Headache

Where p is a random sample from the beta (15, 100) distribution, q is a random sample from the beta (34, 66) distribution, r is a random sample from the beta(33,33) distribution, s is a random sample from the beta (16, 17) distribution, t is a random sample from the beta (10, 7) distribution, u is a random sample from the beta (1, 6) distribution. However, since alpha for u is below 5, 0.5 is added to both alpha and beta, such that u is a random sample from the beta (1.5, 6.5) distribution.

Our original suggestion that 1/7 should be added to each transition was therefore an incorrect simplification of this approach.