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

ERG critique of Allergan Addendum to Additional Analyses

March 18 2012

The MSQ utility mapping function and the HDPM health state of the model

Allergan data of the 24ᵗʰ February 2012 and the 13ᵗʰ March 2012

Allergan in its response of the 13 March 2012 has supplied the mean parameter values for the 3+ patient group for the MSQ utility mapping functions within the modelling. Since the mapping functions are linear in parameter values, applying the mean parameter values should give rise to the mean HRQoL estimates.

Note that the mean MSQ values supplied by Allergan in the 13ᵗʰ of March 2012 response are not entirely consistent with those reported in Table 15 of the Allergan response of the 24ᵗʰ February 2012. The source of these discrepancies is not clear, but they are not large.

The resulting HRQoL values differ slightly between the Allergan response of the 24ᵗʰ February 2012 and the Allergan in the 13ᵗʰ of March 2012.

HRQoL values at 24 weeks by Allergan response date

| | 24ᵗʰ Feb 2012 response | | | | | 13ᵗʰ Mar 2012 response | | |
| | N | | HRQoL | | | HRQoL | | |
Health State	Botox	Placebo	Botox	Placebo	net	Botox	Placebo	net
HS1	24	13	0.691	0.669	0.022	0.692	0.669	0.022
HS2	45	40	0.699	0.638	0.061	0.699	0.638	0.061
HS3	36	44	0.635	0.565	0.070	0.642	0.580	0.062
HS4	26	36	0.561	0.550	0.011	0.549	0.536	0.012
HS5	18	21	0.462	0.597	-0.135	0.465	0.586	-0.122
HS6	15	41	0.501	0.461	0.040	0.501	0.460	0.040

The reasons for this are not clear, but it may lie in the treatment of missing values. Allergan has clarified that only patients with the complete data set required for the MSQ utility mapping function at week 24 were included in the calculation of utilities. The ERG requested the mean parameter values, which for a given parameter may average across some patients with missing values for other parameters. Allergan in its response of the 13ᵗʰ of March has calculated the HRQoL in line with the ERG request.

The HRQoL values of the 24ᵗʰ of February underlie the revised cost effectiveness estimates assessed in the ERG commentary on the Allergan document. For the 30% negative stopping rule coupled with the other non-HRQoL changes to the base case this resulted in a cost effectiveness estimate of £16,214 per QALY. Applying the HRQoL estimates of the 13ᵗʰ of March results in a cost effectiveness estimate of £15,751 per QALY.

The remainder of this document only considers the values supplied by Allergan in the 13ᵗʰ March 2012 response.

MSQ and other data underlying the HRQoL values

The coefficients of the MSQ mapping functions, the mean parameter values and the resultant HRQoL values are presented overleaf. The HRQoL values are presented separately for the intercept value, the three MSQ dimensions related value and the other variables related value prior to be summed to give the overall total HRQoL value for a given arm and health state.

Botox arm 3+ MSQ HRQoL mapping function data

	Episodic migraine				Chronic migraine			
	Coef	HS1	HS2	HS3	Coef	HS4	HS5	HS6
Intercept	0.4509				0.1409			
MSQ-RP	0.0023	79.60	76.10	61.30	0.0056	61.00	47.50	48.30
MSQ-RR	-0.0001	71.00	63.40	44.60	0.0011	46.50	33.00	35.60
MSQ-EF	0.0019	72.50	68.10	54.10	0.0002	52.80	37.40	33.30
Age	-0.0001	42.20	42.00	41.10	0.0021	45.50	39.40	43.60
Male	-0.0073	0.08	0.04	0.14	-0.0043	0.00	0.06	0.20
Caucasian	0.0163	0.96	0.93	0.92	-0.0514	0.96	0.89	0.93
Employment	0.0689	0.79	0.80	0.81	0.1317	0.65	0.56	0.73
Headache medication	-0.0287	1.00	1.00	1.00	-0.0300	1.00	1.00	1.00
Pain condition	-0.1490	0.13	0.02	0.08	-0.1155	0.15	0.00	0.07
Vascular condition	-0.0160	0.25	0.11	0.22	-0.0237	0.19	0.28	0.27
Psychiatric condition	-0.1443	0.46	0.42	0.33	-0.1695	0.54	0.44	0.40
Other condition	-0.0210	1.00	1.00	1.00	0.0159	1.00	1.00	1.00
HRQoL								
Intercept		0.451	0.451	0.451		0.141	0.141	0.141
MSQ HRQoL		0.314	0.298	0.239		0.403	0.310	0.316
Other HRQoL		-0.073	-0.050	-0.048		0.005	0.014	0.043
Total		0.692	0.699	0.642		0.549	0.465	0.501

Within the botox arm among episodic migraine patients for the MSQ dimensions there is no non-monotonicity. Between the episodic migraine health state of HS3 and the chronic migraine health state of HS4 there is non-monotonicity in the MSQ role restrictive dimension of the MSQ. Among chronic migraine patients non-monotonicity arises in the MSQ role-preventive and the MSQ role restrictive dimensions of the MSQ. The overall MSQ contribution to HRQoL shows a slight non-monotonicity between HS5 and HS6.

Placebo arm 3+ MSQ HRQoL mapping function data

	Episodic migraine				Chronic migraine			
	Coef	HS1	HS2	HS3	Coef	HS4	HS5	HS6
Intercept	0.4509				0.1409			
MSQ-RP	0.0023	73.50	70.40	54.00	0.0056	57.20	58.60	51.20
MSQ-RR	-0.0001	60.90	52.60	39.40	0.0011	42.60	37.60	32.20
MSQ-EF	0.0019	60.00	56.30	46.20	0.0002	43.90	37.50	42.60
Age	-0.0001	44.20	45.20	41.50	0.0021	43.40	42.20	42.00
Male	-0.0073	0.23	0.15	0.18	-0.0043	0.19	0.05	0.12
Caucasian	0.0163	0.92	0.90	0.98	-0.0514	0.94	0.86	0.95
Employment	0.0689	0.77	0.70	0.52	0.1317	0.72	0.76	0.54
Headache medication	-0.0287	1.00	1.00	1.00	-0.0300	1.00	1.00	1.00
Pain condition	-0.1490	0.08	0.08	0.05	-0.1155	0.17	0.00	0.15
Vascular condition	-0.0160	0.23	0.25	0.20	-0.0237	0.17	0.24	0.29
Psychiatric condition	-0.1443	0.38	0.48	0.45	-0.1695	0.47	0.33	0.49
Other condition	-0.0210	1.00	1.00	1.00	0.0159	1.00	1.00	1.00
HRQoL								
Intercept		0.451	0.451	0.451		0.141	0.141	0.141
MSQ HRQoL		0.277	0.264	0.208		0.376	0.377	0.331
Other HRQoL		-0.058	-0.076	-0.079		0.020	0.068	-0.011
Total		0.669	0.638	0.580		0.536	0.586	0.460

Within the placebo arm, non-monotonicity occurs between the episodic migraine health state of HS3 and the chronic migraine health state of HS4 in the MSQ role preventive and the MSQ role restrictive dimensions of the MSQ. Among chronic migraine patients non-monotonicity arises in the MSQ role-preventive and the MSQ emotional function dimensions of the MSQ. The overall MSQ contribution to HRQoL shows a very slight non-monotonicity between HS4 and HS5.

For both the botox arm and the placebo arm the other variables contribute additional noise to the final HRQoL values. More particularly, these variables tend to

- reduce the HRQoL differential between botox and placebo for HS1
- increase the HRQoL differential between botox and placebo for HS2
- increase the HRQoL differential between botox and placebo for HS3
- reduce the HRQoL differential between botox and placebo for HS4
- reduce the HRQoL differential between botox and placebo for HS5
- increase the HRQoL differential between botox and placebo for HS6

There is no immediately obvious reason why these parameters should be differentiated between the health states, unless botox is anticipated to have an effect upon these compared to placebo. Equalising these other variables at the average values reported above[1] results in the following HRQoL values.

HRQoL values equalising the values of the contributing non-MSQ parameters

	Botox	Placebo	net
HS1	0.695	0.658	0.037
HS2	0.679	0.645	0.034
HS3	0.620	0.589	0.031
HS4	0.575	0.548	0.027
HS5	0.482	0.549	-0.067
HS6	0.488	0.502	-0.014

This results in some non-monotonicity for HS5 in the botox arm and minimal non-monotonicity in the placebo arm. Applying these HRQoL values worsens the cost effectiveness estimate from £15,751 per QALY to £18,895 per QALY.

Further considerations around non-monotonicity in the MSQ and HRQoL

When assessing of the reasonableness of the non-monotonicity in the above utility functions it should be borne in mind that the health states are defined in terms of HDPM while the utility mapping function is related to the MSQ.

The manufacturer supplied a utility function based upon only HDPM, as summarised within table 47 of the ERG report. This utility function gave rise to HRQoL values which were monotonic in the HDPM defined health states of the model, and which showed minimal HRQoL differences between the arms for a given health state.

The manufacturer argument was that the utility function defined solely in terms of HDPM missed significant elements of the underlying condition, such as the severity and duration of headaches.

If the HDPM and the MSQ were perfectly correlated there would be little point in applying the MSQ based mapping function. The rationale for applying the MSQ utility mapping function within the modelling is that it picks up elements of the underlying condition that are missed by a simple count of HDPM. Given this it is perhaps not be surprising if some apparently perverse results arise from the application of the MSQ based mapping function when viewed narrowly through the prism of the HDPM.

Imposing non-monotonicity upon the MSQ and HRQoL

If the AC is of the opinion that non-monotonicity of HRQoL values derived from the MSQ over health states defined in terms of HDPM remains a major issue, the most practical assumption might be to restrict the individual MSQ dimensions to being monotonic or at least non-decreasing.

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[1] Not weighting by patient numbers within these health states. This results in no change to the intercept HRQoL contribution or the MSQ dimensions HRQoL contribution, but sets the other variables HRQoL contribution to a constant -0.070 in episodic migraine and 0.031 in chronic migraine.

There are a number of permutations that could achieve this, but three general approaches could be adopted. The non-monotonic value could:
- set to the mean of the values of the left superior health state and right inferior health state
- levelled left to the value of the left superior health state
- levelled right to the value of the right inferior health state

MSQ-dimension values for monotonicity

Arm	Health state	MSQ dimension	Original	Mean	Level left	Level right
Botox	HS3	Role restrictive	44.6	54.95	63.4	46.5
Botox	HS5	Role preventive	47.5	54.65	61.0	48.3
Botox	HS5	Role restrictive	33.0	41.05	46.5	35.6
Placebo	HS3	Role preventive	54.0	63.80	70.4	57.2
Placebo	HS3	Role restrictive	39.4	47.60	52.6	42.6
Placebo	HS5	Role preventive	58.6	54.20	57.2	51.2
Placebo	HS5	Role restrictive	37.5	43.25	43.9	42.6

Applying the common set of "other" parameter values across arms and health states, these result in the following HRQoL values.

HRQoL values from monotonic MSQ-dimension values

	Mean			Level left			Level right		
	Botox	Placebo	net	Botox	Placebo	net	Botox	Placebo	net
HS1	0.695	0.658	0.037	0.695	0.658	0.037	0.695	0.658	0.037
HS2	0.679	0.645	0.034	0.679	0.645	0.034	0.679	0.645	0.034
HS3	0.619	0.611	0.009	0.618	0.625	-0.007	0.620	0.596	0.024
HS4	0.575	0.548	0.027	0.575	0.548	0.027	0.575	0.548	0.027
HS5	0.530	0.525	0.005	0.572	0.542	0.030	0.489	0.508	-0.019
HS6	0.488	0.502	-0.014	0.488	0.502	-0.014	0.488	0.502	-0.014

The cost effectiveness estimate changes from £18,895 per QALY to:
- £17,800 per QALY with the mean approach
- £18,256 per QALY with levelling left
- £17,278 per QALY with levelling right