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ORIGINAL RESEARCH

Cost-effectiveness analysis of abobotulinumtoxinA for the treatment of cervical dystonia in the United Kingdom

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Background: Cervical dystonia (CD) involves painful involuntary contraction of the neck and shoulder muscles and abnormal posture in middle-aged adults. Botulinum neurotoxin type A (BoNT-A) is effective in treating CD but little is known about its associated cost-effectiveness.

Objective: To evaluate the cost-effectiveness of abobotulinumtoxinA for treating CD from the UK payer perspective.

Methods: A Markov model was developed to evaluate the cost-effectiveness of abobotulinumtoxinA versus best supportive care (BSC) in CD, with a lifetime horizon and health states for response, nonresponse, secondary nonresponse, and BSC in patients with CD (mean age: 53 years; 37% male). Clinical improvement measured using Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was mapped to utility using data from a randomized trial of abobotulinumtoxinA. Health care resource use, costs, and other inputs were from the British National Formulary, Personal Social Services Research Unit, published literature, or expert opinion. Costs and outcomes were discounted at 3.5% per annum.

Results: In the base case, the incremental lifetime quality-adjusted life-years (QALYs) gained from abobotulinumtoxinA arm versus BSC was 0.253 per patient, whereas the incremental cost was £7,160, leading to an incremental cost-effectiveness ratio (ICER) of £30,468 per QALY. One-way sensitivity analyses showed that these results were sensitive to the proportion of responders to abobotulinumtoxinA at first injection, duration between injections, the number of reinjections allowed among primary nonresponders, and any difference in baseline TWSTRS value between the BSC and abobotulinumtoxinA arms. Probabilistic sensitivity analysis showed that abobotulinumtoxinA was cost-effective 46% and 49% of times at thresholds of £20,000 and £30,000 per QALY, respectively. Scenarios are considered including vial-sharing, productivity losses, secondary response/nonresponse at subsequent injections, 5-year time horizon, and alternative reinjection intervals for BoNT-As produced ICERs ranging from cost-saving to £40,777 per QALY, versus BSC.

Conclusion: AbobotulinumtoxinA was found to be cost-effective in treating adults with CD, at acceptable willingness-to-pay thresholds in the UK.

Keywords: cost-effectiveness analysis, cervical dystonia, botulinum neurotoxin type A, abobotulinumtoxinA

Introduction

Dystonia is a disorder that causes involuntary contraction of skeletal muscles, abnormal posture, and severe pain or discomfort. Dystonia may be more common than evidence suggests, owing to under-recognition, misdiagnosis, or late clinical presentation.[1,2] Cervical dystonia (CD) is the most commonly reported type and mainly affects neck

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and shoulder muscles in middle-aged patients.[3–5] CD's prevalence in Europe seems to exceed than elsewhere (e.g., up to 233 cases per 1,000,000 population[6] vs 89 per 1,000,000 in the US[7]). Within the UK specifically, data have suggested that there are up to 24,000 cases[8] although, interestingly, a much higher estimate (up to 70,000 cases) has been proposed by the Dystonia Society.[9] Data on the associated economic burden of CD are scarce. However, 6-month costs for the US have been estimated as $1,255 to $63,320.[8] Evidence on lost productivity due to work absenteeism is also sparse, although employment statistics show that at least one-third of patients with CD stop working as the disease progresses.[10]

Conventional therapeutic options for CD include skeletal muscle relaxants, anticholinergics, and rehabilitative therapy. In addition, some patients need deep brain stimulation therapy and selective peripheral denervation.[4] Pharmacotherapy involving botulinum neurotoxin type A (BoNT-A) injection has also proven effective[11,12] for CD, especially when combined with conventional therapy. By reducing muscle force, such treatment can alleviate pain, increase the range of free movement, and improve resting posture. Consequently, BoNT-A therapy can reduce the everyday care burden of managing CD[13] and also improves patients' and potentially, caregivers' quality of life (QoL). BoNT-A usage for CD has also been shown to result in productivity-related gains through decreased absenteeism and sickness leave.[14] Also, another study found that, compared with patients on oral medications, more of those on BoNT-A treatments had improvement in employment status (oral medications: 18.5%; BoNT-As: 66.1%) and restoration of full employment with normal productivity (oral medications: 0%; BoNT-As: 12.9%).[15] Such results may reflect BoNT-As' ability to reduce pain and bring about functional improvements in patients with CD, given the strong association between pain and physical dysfunction with job impairment.[16]

These findings invite questions about the comparative effects of the various BoNT-As available. Currently, three such products are used for CD in the UK: abobotulinumtoxinA (Dysport®: Ipsen Limited, Slough, UK), onabotulinumtoxinA (Botox®: Allergan Limited, Marlow, UK), and incobotulinumtoxinA (Xeomin®: Merz Pharmaceuticals GmbH, Frankfurt/Main, Germany). Of note, although no published head-to-head trials have compared the effectiveness of these BoNT-As, a recent mixed treatment comparison reported similar improvements in scores on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS; which comprises three independently scored subscales [severity, disability, pain] , with the three scores being summed to give the TWSTRS total score [range 0–87, best to worst][17]).[18,19] However, evidence also suggests that these BoNT-As differ in key characteristics, including time to first improvement, maximum benefit derived by patients, duration of symptomatic relief, and costs.[8,20] This lack of clarity about the relative merits of different BoNT-As in CD is echoed by other key unknowns regarding these drugs. In particular, despite the significant costs of CD to the UK National Health Service(NHS),[8] there are no published UK data on the associated productivity losses of patients not treated with BoNT-As nor on the cost-effectiveness of these treatments. Little or no evidence exists on cost-effectiveness of BoNT-As for CD in the UK, although one study[21] showed BoNT-As to be cost-effective over a 1-year time horizon relative to BSC from the US government perspective.

With such data gaps in mind, we used economic modeling to assess the cost-effectiveness of abobotulinumtoxinA and other BoNT-As versus best supportive care (BSC) as treatment for CD, from the perspective of the UK NHS and Personal Social Services (PSS). For these purposes, BSC comprised oral medications (including benzodiazepines, baclofen, and anticholinergic agents), deep brain stimulation, and selective peripheral denervation.

Methods

Overview

Ethical permission was not required for this study as it was based purely on secondary data. A Markov model[22,23] with a 3-month cycle duration was developed in Microsoft Excel® (2010) to predict the costs, benefits, and incremental cost-effectiveness ratios (ICERs) per life-year and quality-adjusted life-year (QALY) from initiation of BoNT-A therapy or BSC over an analytic time horizon (lifetime in base case; varied in scenario analyses) or until death. The analysis adopted the perspective of the UK NHS and PSS. Model costs and outcomes were discounted at 3.5% per annum based on the National Institute for Health and Care Excellence reference case.[24] The currency year for the analyses was 2013.

Key characteristics of the population in the model were intended to closely match those in an abobotulinumtoxinA trial.[25] In this study, the mean age was 53.0 years (standard deviation [SD]: 13.0 years); 37% were males and the mean baseline total TWSTRS score was 44.9 (SD: 8.4). As there is no evidence that CD increases mortality risk, the model calculated age-specific mortality using interim life tables from the UK Office for National Statistics.[26]

Model structure

Figure 1 presents the model structure for the BoNT-A and BSC arms, which was informed by consultation with clinical experts. In the BoNT-A arm, patients with CD starting active treatment are divided into two health states: "no response" or "response." Response was defined as an improvement in TWSTRS from baseline of at least 20% at week 4 or 8 or 12, in the base case (higher improvement in TWSTRS from baseline (≥30%) has been tested as part of alternative scenario analysis). Owing to unavailability of data, it was assumed that patients not responding to the initial injection do not achieve response in subsequent injection cycles. Similarly, patients who respond to the initial injection are assumed not to develop secondary nonresponse. Accordingly, only the first injection cycle determines the number of responding and nonresponding patients throughout the model. In an alternative scenario, the model assumed that nonresponders could achieve response with subsequent reinjections given at higher doses. Before treatment discontinuation, nonresponders are allowed up to six BoNT-A reinjections (with electromyographic or ultrasound guidance) before moving to BSC. Initial responders were allowed to receive up to four reinjections before becoming secondary nonresponders and may require investigations (a frontalis or anti-BoNT-A antibody titer test) to determine whether they are resistant to the BoNT-A, before they move to BSC. The enforced discontinuation after these cycles of nonresponse is modeled using tunnel states in the Markov design. Additionally, patients receiving BoNT-A may discontinue treatment due to causes such as loss of effect, severe adverse events (AEs), or other reasons according to an annual discontinuation rate. Once patients discontinue treatment, they move on to BSC. At all health states, patients can die. In the nonactive treatment (BSC) arm, patients start and remain in BSC state until death.

Dysphagia is a commonly reported AE that may impair the patient's QoL or carry certain management costs. Disutility and costs associated with dysphagia were included in the model for the proportion of patients who experience it, but it was assumed not to cause treatment discontinuation.

Model inputs

Efficacy inputs

Data on clinical efficacy (improvements in TWSTRS) were derived from the Phase III placebo-controlled trial

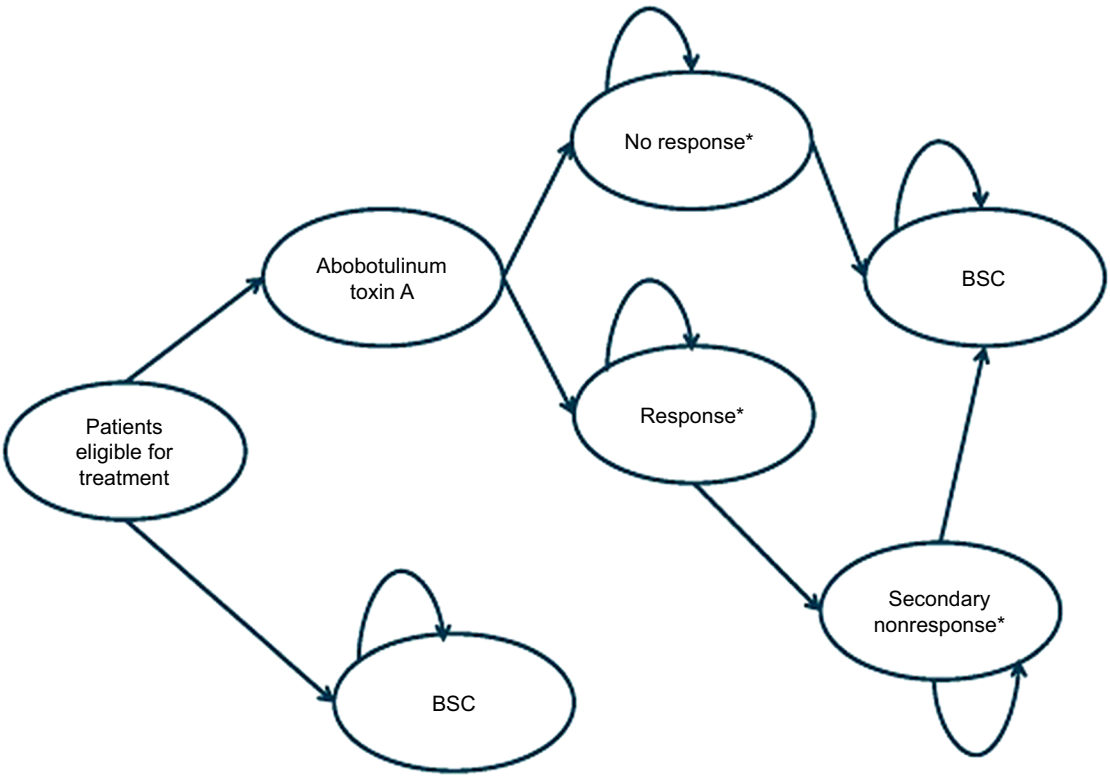

Figure 1 Model structure.
Notes: *Level of response is based on average change of TWSTRS from baseline in the three groups from trial reanalysis. TWSTRS and quality of life are tracked for each health state. All patients at any state are at risk of death.
Abbreviations: BSC, best supportive care; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

of abobotulinumtoxinA (NCT00288509).[25] In this study, compared with placebo, a abobotulinumtoxinA produced significant decreases from baseline in the mean TWSTRS total scores compared with placebo at week 4 (−15.6, SD: 2.0 vs −6.7, SD: 2.0; $p<0.001$) with significant improvements sustained to week 12 (−9.1, SD: 1.7 vs −4.9, SD: 1.7; $p=0.019$).[25] The model assumed that within a model cycle, which was set to be equal to one injection cycle, responders to BoNT-A could experience a sharp improvement in the total TWSTRS score by week 4, with this peaking at week 8, and then waning by week 12. It also assumed that the TWSTRS score at the end of each cycle did not return fully to the baseline value due to residual benefit from BoNT-A as shown in Figure S1. It was also assumed that patients on BSC could benefit from minor improvements in TWSTRS compared to baseline.

Other clinical inputs such as reinjection interval, annual rate of all-cause treatment discontinuation, and AE rates for dysphagia per injection are given in Table S1, with corresponding assumptions.

Utility inputs

For the model, death was assigned a utility of 0 and 1 represented a state of perfect health. Utility data were derived from the Phase III trial of abobotulinumtoxinA.[25] Specifically, the relationship between TWSTRS and utility was determined using a repeated-measures logistic regression analysis on the 36-item Short Form Health Survey and TWSTRS data at baseline or week 12 (Table S2, Figure 2). A preference-based value set was applied to patient responses to the 36-item Short Form Health Survey to obtain utilities. In the model, utility was linked at all times to the TWSTRS score such that improvement or worsening of TWSTRS corresponded with an increasing or decreasing utility. The calculated baseline utility and utility gains at weeks 0, 4, 8, and 12 are detailed in Table 1.

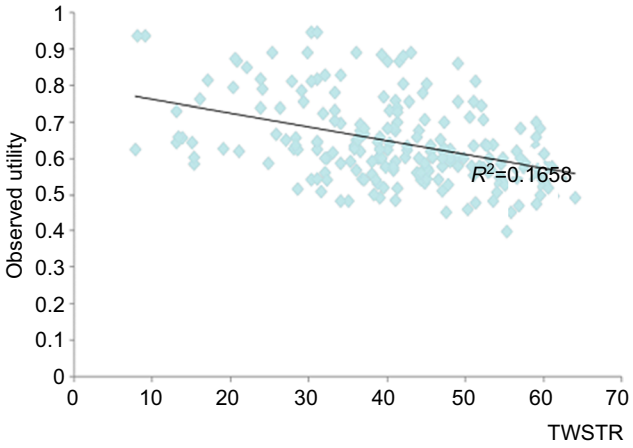

Figure 2 Graphical representation of linkage between utility and TWSTRS estimated from analysis of abobotulinumtoxinA trial. Data extrapolated from a previous study.[25]
Notes: The line represents the best fit to the available data given by the blue points showing reduced utility with higher TWSTRS total score.
Abbreviation: TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

Table 1 Discounted costs and health outcomes in base-case analysis

Costs	**AbobotulinumtoxinA (£)**	**BSC without BoNT-A injections (£)**	**Incremental (AbobotulinumtoxinA vs BSC) (£)**
Drug cost	5,188	0	5,188
Concomitant medications cost	429	488	−59
Drug administration cost	4,600	0	4,600
Disease management cost	6,300	8,869	−2,569
Indirect cost	–	–	–
Total cost	16,517	9,357	7,160
Health outcomes	**AbobotulinumtoxinA**	**BSC without BoNT-A injections**	**Incremental**
Life-years	18.042	18.042	0.000
QALYs	11.970	11.735	0.235
Mean treatment duration with BoNT-A (years)		**AbobotulinumtoxinA**	
Mean treatment duration (years)		10.309	
Nonresponders		0.575	
Responders		9.734	
Cost-effectiveness results		**AbobotulinumtoxinA vs BSC without BoNT-A injections**	
Incremental QALYs gained		0.235	
Incremental costs		£7,160	
Incremental cost per QALY (ICER)		**£30,468**	

Abbreviations: BoNT-A, botulinum neurotoxin type A; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Table 2 Direct and indirect costs (please refer to Table S1 for further details on the base-case model inputs)

Costs	Details	Source/assumptions
Direct costs		
Drug costs	£154 per 500 unit vial at initial dose of BoNT-A, 750 units at subsequent doses; £0 for BSC	Dose varied between first injection and reinjections, as well as among health states with different response levels (nonresponders and responders). Model inputs for drug costs were derived from the BNF,[34] the SmPC of BoNT-A products,[27–29] and expert clinical input
Drug administration costs	£146 per neurologist visit for each cycle of BoNT-A; £0 for BSC	Incurred for each injection according to the treating health care professional who administered the BoNT-A injection and the frequency of treatments. Estimated using costs from the PSS,[35] frequency of visits from the US ANCHOR-CD study (Ipsen Pharma, unpublished data, 2012), and UK clinical experts
Disease management costs	£138 per year for BoNT-A; £493 per year for BSC	Hospitalizations, surgery, or health care professional visits that arise in addition to BoNT-A administration visits or costs of not being treated with BoNT-As. Calculated based on costs derived from Unit Costs of Health and Social Care 2011" published by PSS in the UK and "National Schedule of Reference Costs Year 2010–2011" published by Department of Health in the UK.[35] Frequency of disease management interventions was based on consultation with clinical experts in the UK
Indirect costs*		
Productivity loss	Average hourly wage was £12.76. Number of hours lost per week: 2 hours for BoNT-A; 5 hours for BSC	Indirect costs per week were estimated by multiplying the lost productivity time by the average hourly income in the UK. Average hourly wage was based on data from the ONS[26] and the number of hours lost derived from published literature[30]

Note: *Indirect costs are only included as part of alternative scenario analysis.
Abbreviations: ANCHOR-CD, AbobotulinumtoxinA Neurotoxin: Clinical and Health Economics Outcomes Registry in Cervical Dystonia; BNF, British National Formulary; BoNT-A, botulinum neurotoxin type A; BSC, best supportive care; ONS, Office for National Statistics; PSS, Personal Social Services; SmPC, summary of product characteristics.

Resource use and cost inputs

Direct medical costs in the model comprised the value of all goods, services, and other resources involved in providing the intervention and all current and future consequences linked to the disease process. These included primarily drug costs, administration costs, and disease management costs as outlined in Table 2. All other resources used, concomitant medication costs, and unit costs are detailed in Table S1. In particular, the model assumed that the drug dose varied between first injection and reinjections, as well as among health states with different response levels (nonresponders and responders). Reinjections were associated with a higher dose than first injection, as real-world treatment patterns indicate that doctors normally start with the lowest dose and increase it gradually in subsequent injections if the patient does not respond. Consequently, nonresponders have a higher average dose than responders. Model inputs for first injection were obtained from the summary of product characteristics (SmPC) for each BoNT-A,[27–29] while doses and treatment intervals for subsequent injections were those suggested by clinical experts.

Drug administration costs were incurred for each injection according to the health care professional who gave the BoNT-A injection and the frequency of treatments. Concomitant medication costs were incurred for medications used by patients with CD in addition to BoNT-A therapy. Disease management costs comprised those of hospitalizations, surgery, or health care professional visits required additionally to those for BoNT-A administration.

Indirect costs primarily included costs associated with productivity losses of patients with CD. To quantify the economic impact of productivity losses, lost productive time (LPT) from Stacy et al (2012)[30] was used to estimate the per-person hours per week associated with reduced performance at work ("presenteeism") and absence from work ("absenteeism") due to disability. The associated indirect costs per week were estimated by multiplying the LPT by the average hourly income in the UK (given in Table S1). Due to unavailability of data, indirect costs for time to doctor office visits and for caregivers' time were not considered.

Analyses

Base-case analysis

The base-case analysis compared the costs and QALYs, discounted at 3.5%, of using abobotulinumtoxinA versus BSC, from the NHS and PSS perspective over a lifetime horizon in a scenario where response is considered as at least 20% improvement in TWSTRS total score from

baseline and vial-sharing was not allowed. The base-case model parameters are presented in Table S1 alongside their assumptions, with the exception of indirect costs, which were considered only in an alternative scenario analysis described ahead.

Alternative scenario analysis

Alternative scenario analyses were conducted to test the following assumptions: productivity losses incurred by patients with CD; sharing of vials; analytic time horizon of 5 years; injection cycles as in the SmPCs, specifically, 16 weeks for abobotulinumtoxinA,[28] 10 weeks for incobotulinumtoxinA,[29] 10 weeks cycle for onabotulinumtoxinA[27]; at least 30% improvement in TWSTRS from baseline and allowance of secondary nonresponse following the initial BoNT-A injection, or achievement of response at subsequent injection cycles for initial nonresponders. The following comparisons were also performed: onabotulinumtoxinA versus BSC; incobotulinumtoxinA versus BSC; abobotulinumtoxinA versus onabotulinumtoxinA; and abobotulinumtoxinA versus incobotulinumtoxinA.

One-way sensitivity analysis

To identify model drivers and examine key areas of uncertainty within the model, one-way sensitivity analyses were provided for all major model variables. Parameters were varied between a minimum and maximum range that was determined directly from published data. Where data were not available to inform this range, the minimum and maximum values were ±20% of the base-case value. Tornado diagrams were generated for incremental costs, incremental QALYs and ICERs, and incremental net benefit using a £20,000/QALY threshold. Table S3 lists the parameters varied in one-way sensitivity analysis.

Probabilistic sensitivity analysis

To account for multivariate and stochastic uncertainties in the model, a probabilistic sensitivity analysis was performed. Probabilistic parameters were defined according to appropriate statistical distributions to ascertain uncertainty. The selection of distributions was dependent on the nature of the underlying parameter, with beta distribution being used for probabilities and utilities, and gamma distribution used for positively valued parameters such as the costs.

The probabilistic sensitivity analysis was run for 5,000 simulations. The incremental gains in terms of QALYs were plotted against incremental costs of abobotulinumtoxinA and its comparators on the cost-effectiveness plane. A cost-effectiveness acceptability curve was generated to show the probability of being cost-effective for each treatment over a range of willingness-to-pay values for a QALY. Table S4 lists the distribution of parameters varied in probabilistic sensitivity analysis.

Results

Base-case results

The discounted costs and health outcomes for abobotulinumtoxinA and BSC for the base case are given in Table 1. The total incremental QALYs gained from abobotulinumtoxinA compared to BSC was 0.235 per patient, with the total incremental cost being £7,160. This corresponds to an ICER of £30,468 per QALY gained.

Alternative scenario results

The results of abobotulinumtoxinA versus BSC for the alternative scenarios are presented in Table 3. With vial-sharing, the total incremental QALYs gained were unchanged but the associated total incremental costs were £6,234, corresponding to an ICER of £26,526 per QALY (i.e., lower than the base-case ICER). When productivity losses were considered, the QALYs remained unchanged but the total incremental costs were –£7,311, implying that abobotulinumtoxinA usage was cost-saving compared to BSC. Changing the time horizon to 5 years resulted in total incremental costs of £2,809, incremental QALYs of 0.083, and an ICER of £38,117. Considering 5% secondary nonresponders and 25% secondary responders resulted in total incremental QALYs of 0.247, total incremental costs of £10,072, and an ICER of £40,777. With a 16-week reinjection interval for abobotulinumtoxinA,[28] the incremental costs and QALYs were found to be £5,396 and 0.252, respectively, with an associated ICER of £21,413. Considering response as 30% improvement in TWSTRS from baseline resulted in an ICER of £29,089 (i.e., lower than the base-case ICER).

Table S5 presents comparisons of onabotulinumtoxinA and incobotulinumtoxinA versus BSC and abobotulinumtoxinA versus onabotulinumtoxinA and incobotulinumtoxinA for 12- and 10-week reinjection intervals. Compared to BSC, the ICERs for onabotulinumtoxinA and incobotulinumtoxinA were £48,978 and £58,554 for the 12-week injection cycle, and £48,625 and £44,933 for the 10-week interval, respectively, due to higher drug-acquisition costs associated with onabotulinumtoxinA and incobotulinumtoxinA compared to abobotulinumtoxinA.

Table 3 Alternative scenario results: abobotulinumtoxinA compared to BSC

Scenario	AbobotulinumtoxinA		BSC		Incremental (AbobotulinumtoxinA vs BSC)		
	Total costs (discounted)	QALYs	Total costs (discounted)	QALYs	Total costs (discounted)	QALYs	ICERs
Base case	£16,517	11.970	£9,357	11.735	£7,160	0.235	£30,468
Considering 5% secondary nonresponders and 25% secondary responders	£19,429	11.982	£9,357	11.735	£10,072	0.247	£40,777
Considering 16 weeks reinjection interval for abobotulinumtoxinA*	£14,728	11.948	£9,332	11.696	£5,396	0.252	£21,413
Considering response as ≥30% improvement in TWSTRS from baseline	£16,222	11.974	£9,357	11.738	£6,865	0.236	£29,089
Considering indirect costs due to productivity loss	£61,971	11.970	£69,282	11.735	–£7,311	0.235	Cost-saving
Considering vial-sharing	£15,591	11.970	£9,357	11.735	£6,234	0.235	£26,526
Time horizon = 5 years	£5,443	2.942	£2,280	2.859	£2,809	0.083	£38,117

Note: *Same reinjection interval (16 weeks) was assumed for BSC.
Abbreviations: BSC, best supportive care; ICERs, incremental cost-effectiveness ratios; QALYs, quality-adjusted life-years; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

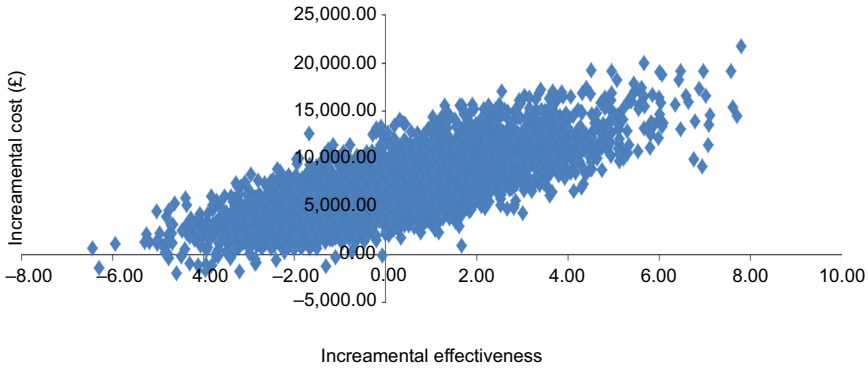

Figure 3 Cost-effectiveness planes of incremental costs per QALY of abobotulinumtoxinA versus BSC.
Abbreviation: BSC, best supportive care; QALY, quality-adjusted life-year.

One-way sensitivity analysis results

One-way (deterministic) sensitivity analysis was conducted on the parameters listed in Table S3. The tornado diagrams given in Figures S2–S5 show the most influential parameters on outcomes for abobotulinumtoxinA versus BSC. Incremental costs were most influenced by the proportion of responders to abobotulinumtoxinA at first injection, duration of the reinjection interval, and the number of cycles of reinjection allowed among primary nonresponders. Incremental QALYs and incremental net benefit were most sensitive to number of cycles of reinjection allowed amongst primary nonresponders and proportion of responders and nonresponders to abobotulinumtoxinA at first injection. ICERs were most sensitive to TWSTRS value at baseline among BSC and abobotulinumtoxinA patients and the number of cycles of reinjection allowed among primary nonresponders.

Probabilistic sensitivity analysis results

Results of the probabilistic sensitivity analysis conducted for the base case are presented in Figures 3 and 4. The cost-effectiveness plane shows that, although abobotulinumtoxinA is more costly than BSC, it is also more effective. The CEAC showed that abobotulinumtoxinA had a 46% probability of being cost-effective at a threshold of £20,000 compared to BSC without BoNT-A injections.

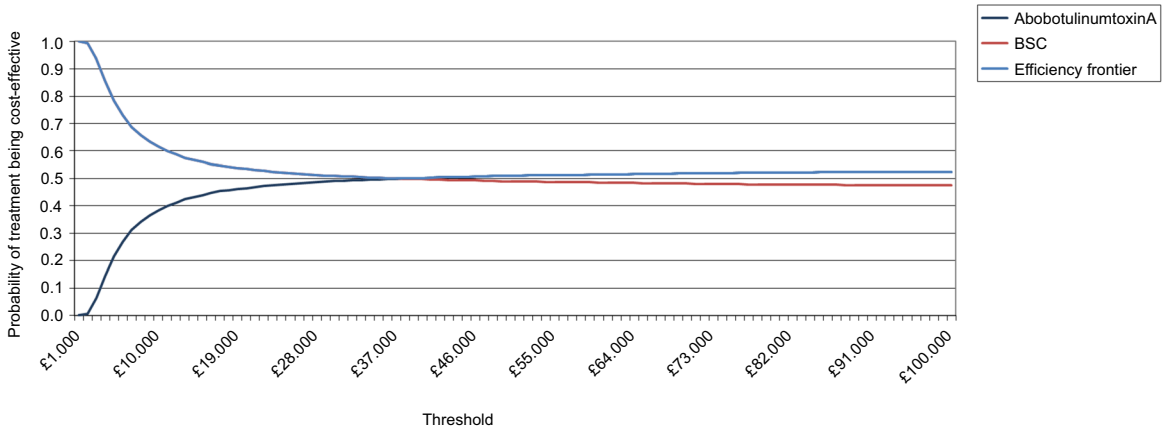

Figure 4 Cost-effectiveness acceptability curves of abobotulinumtoxinA and BSC without toxins injections.
Abbreviation: BSC, best supportive care.

Discussion

Our economic model showed for patients with CD in the UK that abobotulinumtoxinA was cost-effective compared to BSC, at a maximum acceptable willingness-to-pay threshold of £30,000 per QALY[24] under base-case assumptions. Specifically, the treatment provided a lifetime gain of 0.235 QALYs at an incremental cost of £7,160 and the health benefits was attributable to a reduction in the severity of CD (as measured by TWSTRS, which correlated directly with patients' utility). In addition, the results remained broadly consistent in both testing of alternative scenarios to the base cases and across a range of sensitive analyses. Overall, therefore, our findings represent a significant development in the knowledge of the economic and health benefits of using BoNT-As for this indication, given that few other economic evaluations of these treatments for CD have been previously published.[21,31]

As with many models, ours had limitations arising from data availability and structural assumptions. In terms of clinical response, data were available to estimate the proportion of responders and their improvement in TWSTRS total score for the first injection cycle from clinical trial[25] but not for subsequent cycles. Therefore, it was assumed that only the first injection determined response, although in clinical practice additional responses would probably be achieved in subsequent cycles for more patients. Furthermore, there was a lack of data on the quantities of abobotulinumtoxinA administered and health care resources consumed in managing patients. We made the assumption that the utility–TWSTRS relationship, which was estimated based on data from one cycle of botulinum toxin use, would apply equally to subsequent cycles, though we cannot know how this relationship may differ at later times. Having to extrapolate outcomes beyond the timeframe of available clinical data was another unavoidable limitation – one commonly encountered in this type of evaluation.

A key strength of our study is how it took account of productivity gains resulting from effective treatment for CD. The importance of CD's effect on productivity has been recognized previously, although studies have not generally quantified it suitably for subsequent use in economic evaluations. For instance, a study of almost 300 patients by the Finnish Dystonia Association[32] found 97 subjects (39%) had retired because of CD at a median age of 48 years, while many others reported sick leave, reduced productivity, and loss of employment.[14,33] Similarly, a second study found 53.3% of patients with CD reported that employment status was negatively affected through reduced hours or responsibilities, including 18.9% of patients who had lost employment due to CD symptoms.[15]

Another reason that is essential to demonstrate the cost-effectiveness of BoNT-A is that many patients receive inappropriate treatment (e.g., physiotherapy alone), given that CD is an under-recognized condition and BoNT-As are consequently underutilized for CD. To the extent that cost of treatment with BoNT-A is a potential barrier, it is important to communicate the cost-effectiveness of BoNT-A. In conclusion, we believe that in demonstrating the cost-effectiveness of abobotulinumtoxinA as treatment for CD, our study makes a compelling case for wider use in the UK of such therapy that can benefit patients with this physically and psychologically debilitating condition.

Conclusion

The use of abobotulinumtoxinA in adult patients with CD was found to be cost-effective at an acceptable willingness-to-pay threshold in the UK and also provided additional QoL gains. This evidence should help to inform clinical decision making and commissioning where BoNT-A therapy is being considered as a potential treatment for CD.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

MM, SA, and KD are employees of Evidera Inc., which received consultancy fees to conduct the research from Ipsen Pharma. JD and SG are both full-time employees of Ipsen Pharma. TH has received consultancy fees from Ipsen Pharma for work relating to Spasticity management TH has also received honoraria for lectures delivered from Merz and Allergan. Ipsen Pharma did not have any influence on the interpretation of data as well as the final conclusions drawn. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Model inputs

Parameters	Base case				Source/assumptions
	AbobotulinumtoxinA	OnabotulinumtoxinA	IncobotulinumtoxinA	BSC	
Clinical inputs					
Change from baseline of TWSTRS at weeks 4, 8, 12 (mean (SE))					
TWSTRS change from baseline at 4 weeks				–5.0 (2.0)	AbobotulinumtoxinA trial[1]
No response	–0.6 (0.0)	–0.6 (0.0)	–0.6 (0.0)	–	AbobotulinumtoxinA trial [1]
Response	–20.3 (2.0)	–20.3 (2.0)	–20.3 (2.0)	–	OnabotulinumtoxinA and incobotulinumtoxinA are assumed to have same response as abobotulinumtoxinA
TWSTRS change from baseline at 8 weeks				–4.2(2.0)	AbobotulinumtoxinA trial[1]
No response	–0.1 (0.0)	–0.1 (0.0)	–0.1 (0.0)	–	AbobotulinumtoxinA trial[1]
Response	–18.3 (2.0)	–18.3 (2.0)	–18.3 (2.0)	–	OnabotulinumtoxinA and incobotulinumtoxinA are assumed to have same response as abobotulinumtoxinA
TWSTRS change from baseline at 12 weeks				–3.3 (2.0)	AbobotulinumtoxinA trial[1]
No response	–0.2 (0.1)	–0.2 (0.1)	–0.2 (0.1)	–	AbobotulinumtoxinA trial[1]
Response	–9.4 (2.0)	–9.4 (2.0)	–9.4 (2.0)	–	OnabotulinumtoxinA and incobotulinumtoxinA are assumed to have same response as abobotulinumtoxinA
Response rate of first injection for BoNT-A therapies (%)					
Response rate of first injection					
No response	37.0	37.0	37.0		AbobotulinumtoxinA trial[1]
Response	63.0	63.0	63.0		OnabotulinumtoxinA and incobotulinumtoxinA are assumed to have same response as abobotulinumtoxinA
Response rate of subsequent injection for BoNT-A therapies (%)					
Annual rate of response after initial nonresponse (rate per year)	0.0	0.0	0.0		Patients who do not respond at the initial injection do not achieve response in subsequent injection cycles
Annual rate of secondary nonresponse after initial response (rate per year)	0.0	0.0	0.0		Similarly, patients who achieve response at the initial injection do not develop secondary nonresponse
Reinjection interval for BoNT-A therapies (weeks)					
Duration of treatment cycle (weeks)	12.0[#]	12.0[##]	12.0[###]		Assumed to be in line with abobotulinumtoxinA SmPC[2] and experts clinical opinion
Annual rate of all-cause treatment discontinuation (%)					
Discontinuation rate per year					
No response	1.1	1.1	1.1	–	Kessler et al (1999)[3]
Response	1.1	1.1	1.1	–	
Adverse events by BoNT-A therapies (%)					
Dysphagia rate per injection	15	19	13	–	Inferred from SmPCs of BoNT-A products[2,4,5]

(*Continued*)

Table S1 (*Continued*)

Parameters	Base case				Source/assumptions
	AbobotulinumtoxinA	OnabotulinumtoxinA	IncobotulinumtoxinA	BSC	
Utility inputs					
Baseline utility and utility gains (mean)					
	BoNT-A			BSC	Calculated from estimated utility-TWSTRS relationship and TWSTRS data at weeks 0, 4, 8, and 12
Baseline utility				0.6368	
No response	0.6398				
Response	0.6349				
QALYs gain per person for first cycle				0.0026	
No response	0	0	0		
Response	0.0117	0.0117	0.0117		
QALY gain per person for subsequent cycles				0.0035	
No response	0	0	0		
Response	0.0130	0.0130	0.0130		
Resource use and cost inputs					
Drug costs					
Cost per vial	£154.00 per 500 unit vial, £92.40 per 500 unit vial	£276.40 per 200 unit vial, £138.20 per 100 unit vial	£129.90 per 100 unit vial, £72.00 per 50 unit vial	–	BNF[6]
Average dose per cycle: first injection					
Mean dose (units)	500	200	200	–	SmPC of BoNT-A products[2,4,5]
Average dose per cycle: subsequent injections					
Mean dose (units) – no response	750	300	300		Expert clinical input
Mean dose (units) – response	400	133	160		
Drug administration costs and frequency of use of BoNT-A therapies					
	Cost per injection (per visit) for BoNT-A therapies	Frequency of use (for 1 visit per injection) for BoNT-A		Frequency of use (for 1 visit per injection)for BSC	Administration costs were derived from PSS[7] Frequency of visits was collected from Ipsen US ANCHOR-CD study (Ipsen Pharma, unpublished data, 2012) and verified with clinical experts in the UK
Neurologist visit	£146.00	73.5%		NA	
Neurophysiologist visit	£146.00	26.5%		NA	
Nurse visit	£42.00	0.0%		NA	
Concomitant medication costs and frequency of use					
	Unit costs (per mg)	Dose per day (mg)			Unit drug costs and dosing schedule for concomitant medications were obtained from BNF[6]
Anticholinergics	£0.0070	1			
Benzodiazepines	£0.0720	1			
Analgesics	£0.0003	1,000			
Dopamine antagonist	£0.0990	2.5			
Beta blockers	£0.0011	40			
Baclofen	£0.0020	60			

Antiepileptics	£0.0006	600			
Other muscle relaxants	£0.0094	7.5			
Frequency of use (for BoNT-As and BSC)	BoNT-A (%)			BSC (%)	Distribution of frequency of use among different drugs were collected from Ipsen US ANCHOR-CD study (Ipsen Pharma, unpublished data, 2012) and verified with clinical experts in UK
% of patients taking concomitant medications	35			50	
Anticholinergics	0.6			0.6	
Benzodiazepines	23.5			26.5	
Analgesics	33.5			33.5	
Dopamine antagonist	0.6			0.6	
Beta blockers	0.6			0.6	
Baclofen	3.2			3.2	
Antiepileptics	5.8			5.8	
Other muscle relaxants	29.2			29.2	
Disease management costs and frequency of disease management interventions					
	Unit costs	Frequency per year (for BoNT-A)	Frequency per year (for BSC)		The disease management costs were derived from "Unit Costs of Health and Social Care 2011" published by (PSS) in the UK and "National Schedule of Reference Costs Year 2010–2011" published by Department of Health in the UK[7]
Neurologist visit (excluding BoNT-A injection per visit)	£146.00	0	2		
GP visit (per visit)	£53.00	2	2		
Hospitalization (per day)	£428.00	1.5%	1.5%		The frequency of disease management interventions was based on consultation with clinical experts in UK
Average length of stay	–	5	5		
Deep brain stimulation (per surgery)	£4,384.89	NA	1%		
Selective peripheral denervation (per surgery)	£1,867.00	NA	1%		
Indirect costs*					
Median hourly wage in the UK (per hour)	£12.76				Median hourly wage reported by Office for National Statistics Survey for 2013[8]
LPT due to patients with CD and carers combined (number of hours per week)					
Productivity loss	2			5	The model uses LPT due to absenteeism and presenteeismfrom Stacy et al (2012)[9]
Time to doctor office visit	–			–	
Caregiver time	–			–	Indirect costs due to time to doctor office visit and caregiver time are not considered, since no data was available
Total	2			5	

Notes: *Indirect costs are not included in the base case analysis. #For AbobotulinumtoxinA, it is 16 weeks as per AbobotulinumtoxinA SmPC – this is tested as part of scenario analyses, ##For OnabotulinumtoxinA, it is 10 weeks as per OnabotulinumtoxinA SmPC – this is also tested as part of scenario analyses, ###For IncobotulinumtoxinA, it is 10 weeks as per IncobotulinumtoxinA SmPC – this is also tested as part of scenario analyses.

Abbreviations: ANCHOR-CD, AbobotulinumtoxinA Neurotoxin: Clinical and Health Economics Outcomes Registry in Cervical Dystonia; BNF, British National Formulary; BoNT-A, botulinum neurotoxin type A; BSC, best supportive care; GP, general practitioner; LPT, lost productive time; PSS, Personal Social Services; QALYs, quality-adjusted life-years; SE, standard error; SmPC, summary of product characteristics; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; NA, not available.

Table S2 Estimates of statistical model linking utility and TWSTRS based on analysis of abobotulinumtoxinA trial

Parameter	Parameter estimate	Parameter
Intercept	1.255	
Coefficient for TWSTRS	–0.0159	
	Covariance matrix	
	Intercept	**Coefficient for TWSTRS**
Intercept	0.01157	
Coefficient for TWSTRS	–0.000234	5.437E-06

Abbreviations: TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

Table S3 Parameters included in one-way sensitivity analysis

Parameter/variable name	Description	Base-case input	Low value	High value
discH	Discount rate for health (%)	0.035	0.028	0.042
discC	Discount rate for cost (%)	0.035	0.028	0.042
iAge	Age (years)	53.00	42.400	63.600
pMale	Gender (% male)	0.37	0.296	0.444
TWSBline_NonResp	Mean baseline TWSTRS – nonresponders: abobotulinumtoxinA	42.79	34.232	51.348
TWSBline_Resp	Mean baseline TWSTRS – responders: abobotulinumtoxinA	44.12	35.296	52.944
TWSBline_BSC	Mean baseline TWSTRS – BSC	43.63	34.902	52.353
Coeff_TWS	Coefficient for TWSTRS	–0.02	–0.019	–0.013
Coeff_Inter	Intercept	1.26	1.004	1.506
iReinj_PriNonResp	Number of reinjection attempts for primary nonresponders before abandoning treatment	6.00	4.800	7.200
iReinj_SecNonResp	Number of reinjection attempts for secondary nonresponders before abandoning treatment	4.00	3.200	4.800
TWSChangeAt4Wks_Abo_nonresponder	AbobotulinumtoxinA_TWSTRS change from baseline at 4 weeks – nonresponders	–0.61	–0.643	–0.583
TWSChangeAt4Wks_Abo_fullresponder	AbobotulinumtoxinA _TWSTRS change from baseline at 4 weeks – responders	–20.29	–22.290	–18.290
TWSChangeAt8Wks_Abo_nonresponder	AbobotulinumtoxinA _TWSTRS change from baseline at 8 weeks – nonresponders	–0.14	–0.140	–0.136
TWSChangeAt8Wks_Abo_responder	AbobotulinumtoxinA _TWSTRS change from baseline at 8 weeks – responders	–18.30	–20.300	–16.300
TWSChangeAt12Wks_Abo_nonresponder	AbobotulinumtoxinA _TWSTRS change from baseline at 12 weeks – nonresponders	–0.21	–0.283	–0.143
TWSChangeAt12Wks_Abo_fullresponder	AbobotulinumtoxinA _TWSTRS change from baseline at 12 weeks – responders	–9.35	–11.350	–7.350
TWSChangeAt4Wks_BSC	BSC_TWSTRS change from baseline at 4 weeks	–4.97	–6.970	–2.970
TWSChangeAt8Wks_BSC	BSC_TWSTRS change from baseline at 8 weeks	–4.22	–6.220	–2.220
TWSChangeAt12Wks_BSC	BSC_TWSTRS change from baseline at 12 weeks	–3.32	–5.320	–1.320
distriFirstInj_Abo_nonresponder	Probability of nonresponse at first injection	0.37	0.296	0.444
distriFirstInj_Abo_responder	Probability of response at first injection	0.63	0.504	0.756
pAE_Abo	AE rate per injection: abobotulinumtoxinA (%)	15%	12%	18%
dFirstInj_Abo	AbobotulinumtoxinA _first injection dosage: mean dose (unit)	500.00	400.000	600.000
dFirstInj_Ona	OnabotulinumtoxinA _first injection dosage: mean dose (unit)	200.00	160.000	240.000
dFirstInj_Inco	IncobotulinumtoxinA _first injection dosage: Mean dose (unit)	200.00	160.000	240.000
dReinj_Abo_nonresponder	Average abobotulinumtoxinA reinjection dosage: nonresponder (unit)	750.00	600.000	900.000

Parameter/variable name	Description	Base-case input	Low value	High value
dReinj_Abo_responder	Average abobotulinumtoxinA reinjection dosage: responder (unit)	400.00	320.000	480.000
cDrugFirstInj_Abo	AbobotulinumtoxinA _first injection cost (£)	154.00	123.200	184.800
cDrugReinj_Abo_ nonresponder	AbobotulinumtoxinA _reinjections cost – nonresponder (£)	246.40	197.120	295.680
cDrugReinj_Abo_ fullresponder	AbobotulinumtoxinA _reinjections cost – responder (£)	154.00	123.200	184.800
cConMed_BoNTA	Concomitant Meds Cost_BoNTA (£)	0.05	0.042	0.062
cConMed_BSC	Concomitant Meds Cost _BSC (£)	0.07	0.059	0.089
cDrugAdmin	Cost Drug Admin (£)	146.00	116.800	175.200
cDisMgt_Abo	Cost Disease Management_ AbobotulinumtoxinA (£)	31.77	25.419	38.129
cDisMgt_BSC	Cost Disease Management _BSC (£)	113.31	90.645	135.967
cAE	Cost AEs_BoNTA (£)	–	–	–
cIndirect_BoNTA	Cost Indirect_Abo (£)	306.24	244.992	367.488
cIndirect_BSC	Cost Indirect_BSC (£)	765.60	612.480	918.720
timeYearsInCycle_Abo	Reinjection Interval (years)	0.23	0.184	0.276

Abbreviations: AE, adverse event; BoNTA, botulinum neurotoxin type A; BSC, best supportive care; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

Table S4 Parameters included in probabilistic sensitivity analysis

Parameter	Distribution
Utility at each TWSTRS score (based on mapping)	Multivariate normal (Cholesky)
Mean baseline TWSTRS distribution, nonresponders and responders at 0, 4, 8, 12 weeks	Gamma
Transition probability: response to secondary nonresponse	Beta
Duration of treatment cycle: abobotulinumtoxinA	Gamma
Treatment discontinuation rate per year	Gamma
AbobotulinumtoxinA _first injection dosage	Gamma
AbobotulinumtoxinA_ reinjection dosage: nonresponder	Gamma
AbobotulinumtoxinA_ reinjection dosage: responder	Gamma
Setting where drug is administered (distribution)	
Neurologist visit	Beta
Physiotherapist visit	Beta
Nurse visit	Beta
Disease management	
Neurologist visit (excluding BoNT-A injection) per year	Gamma
GP visit per year	Gamma
Hospitalization rate per year: BoNT-A	Beta
Hospitalization rate per year: BSC	Beta
Length of stay for hospitalization: BoNT-A	Gamma
Length of stay for hospitalization: BSC	Gamma

Abbreviations: BSC, best supportive care; BoNT-A, botulinum neurotoxin type A; GP, general practitioner; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

Table S5 Alternative scenario results: other comparisons

Scenario	OnabotulinumtoxinA		BSC		Incremental (onabotulinumtoxinA vs BSC)		
	Total costs (discounted)	QALYs	Total costs (discounted)	QALYs	Total costs (discounted)	QALYs	ICERs
Base case	£20,573	11.964	£9,357	11.735	£11,216	0.229	£48,978
Considering 10 weeks reinjection interval for onabotulinumtoxinA*	£21,968	11.954	£9,277	11.693	£12,691	0.261	£48,625
Scenario	**IncobotulinumtoxinA**		**BSC**		**Incremental (IncobotulinumtoxinA vs BSC)**		
	Total costs (discounted)	**QALYs**	**Total costs (discounted)**	**QALYs**	**Total costs (discounted)**	**QALYs**	**ICERs**
Base case	£22,473	11.959	£9,357	11.735	£13,116	0.224	£58,554
Considering 10 weeks reinjection interval for incobotulinumtoxinA*	£21,364	11.962	£9,277	11.693	£12,087	0.269	£44,933

Note: *Same reinjection interval (10 weeks) was assumed for BSC.
Abbreviations: BSC, best supportive care; ICERs, incremental cost-effectiveness ratios; QALYs, quality-adjusted life-years.

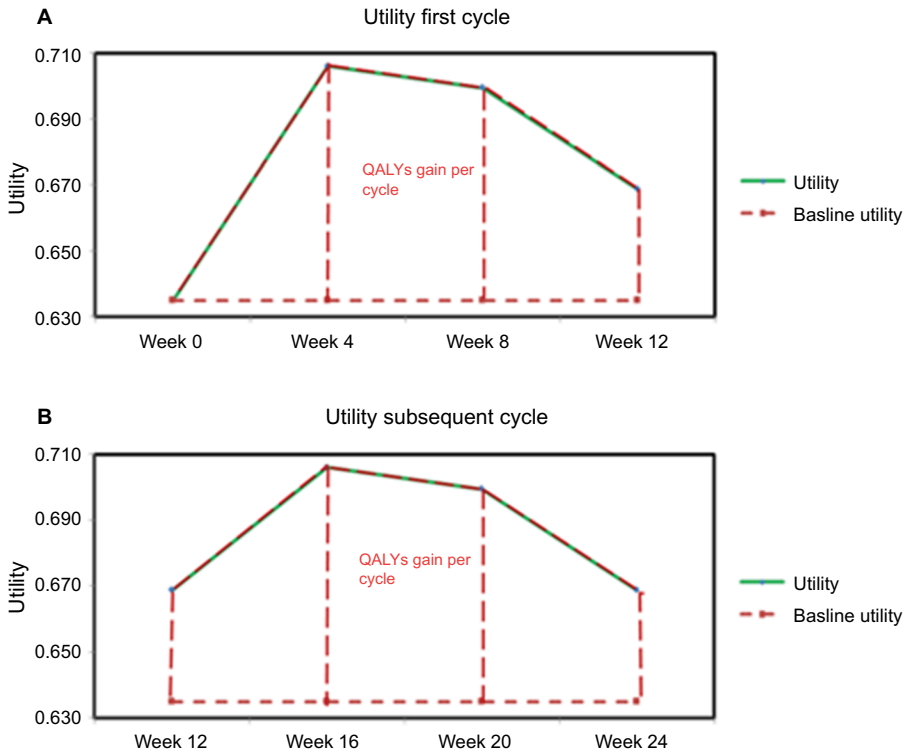

Figure S1 Illustration of QALY gain in first (**A**) and subsequent cycle (**B**) when TWSTRS is assumed to have residual benefit at week 12.
Abbreviations: QALYs, quality-adjusted life-years; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

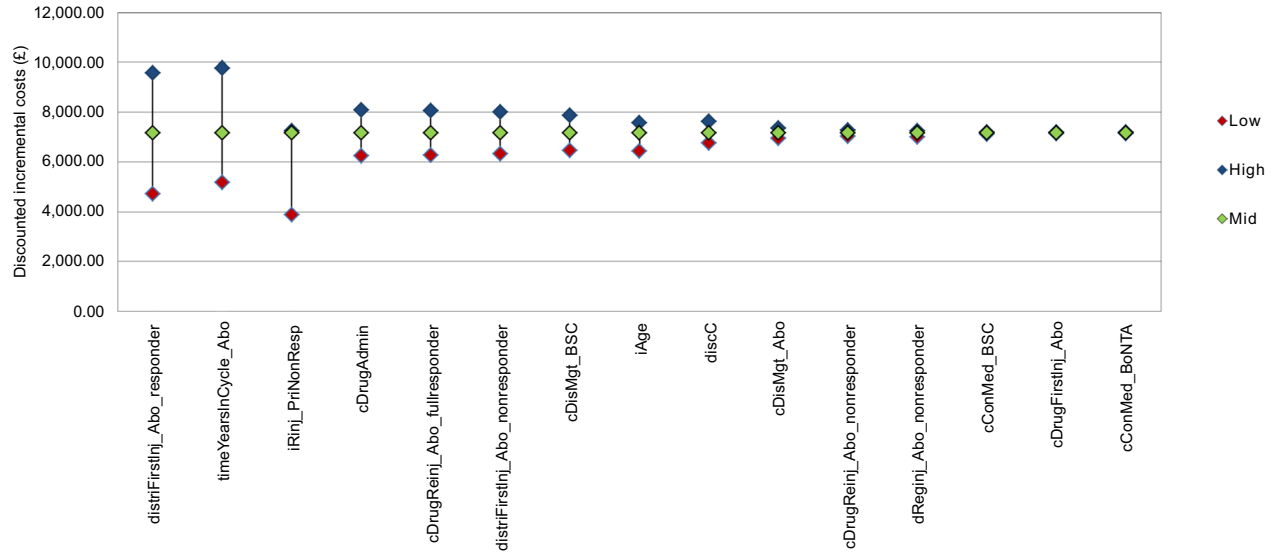

Figure S2 Tornado diagram of one-way sensitivity analysis on incremental cost.
Abbreviations: BSC, best supportive care; BoNT-A, botulinum neurotoxin type A.

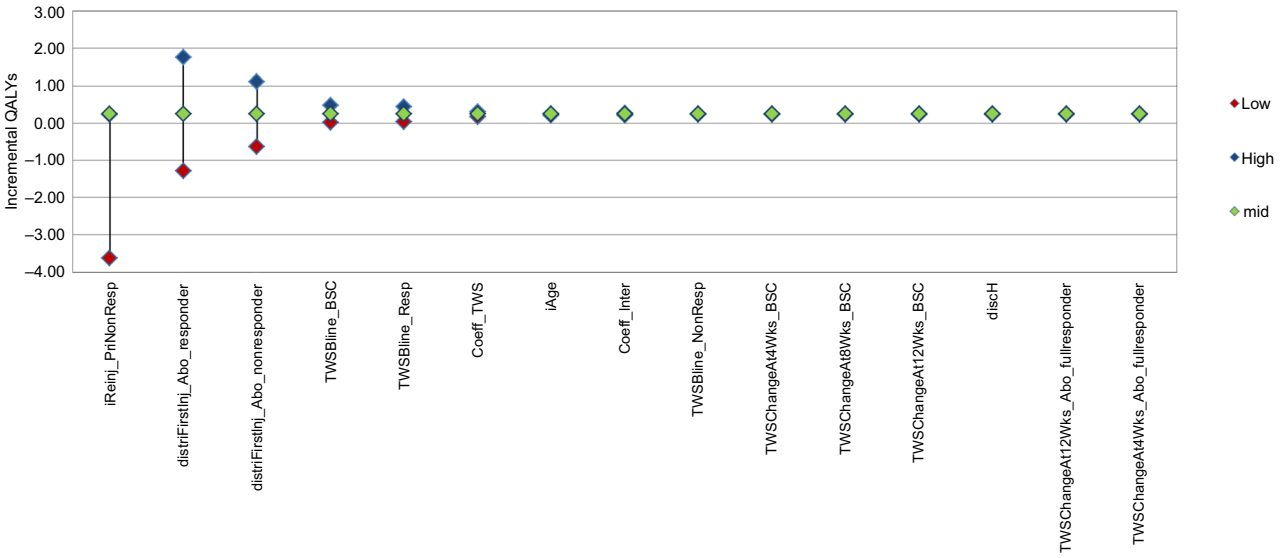

Figure S3 Tornado diagram of one-way sensitivity analysis on incremental benefit.
Abbreviations: BSC, best supportive care; QALY, quality-adjusted life-year; TWS, Toronto Western Spasmodic.

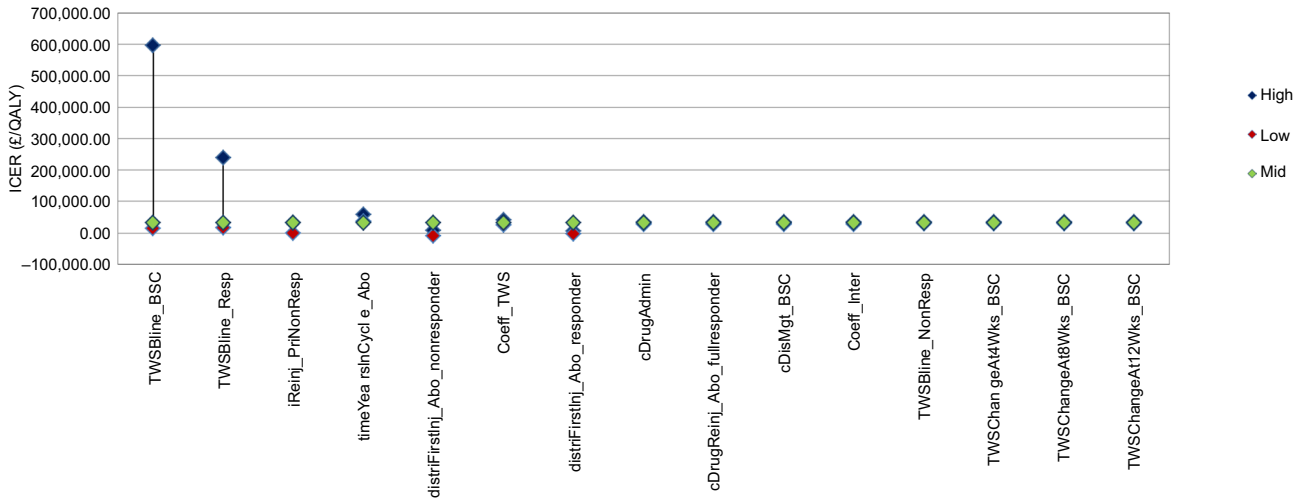

Figure S4 Tornado diagram of one-way sensitivity analysis on ICER.
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; TWS, Toronto Western Spasmodic.

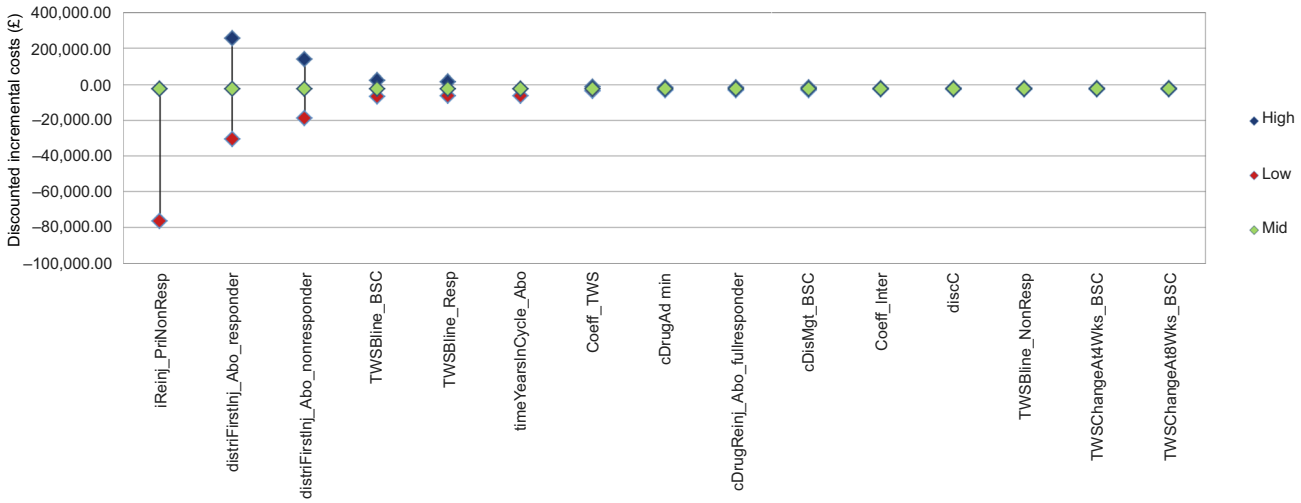

Figure S5 Tornado diagram of one-way sensitivity analysis on incremental net benefit with a willingness-to-pay threshold of £20,000/QALY.
Abbreviations: BSC, best supportive care; INB, incremental net benefit; QALY, quality-adjusted life-year; TWS, Toronto Western Spasmodic.

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