National Institute for Health and Care Excellence

Draft for consultation

Stroke rehabilitation in over 16s (update)

Cost-utility analysis: In people after stroke, what is the clinical and cost effectiveness of botulinum toxin A to reduce spasticity?

NICE guideline GID-NG10175

Economic analysis report

April 2023

Draft for Consultation

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1 Introduction

This is a new area in the guideline. The review protocol includes oral medicines (for example baclofen), intramuscular medicine (botulinum toxin type A [BoNT-A]), intrathecal medicine (baclofen) and interventions such as electrotherapies and acupuncture. The options that are suitable depend on the type and severity of spasticity, and previous treatment failure therefore these options are not all alternatives to each other. The key priority areas identified for further health economic modelling were BoNT-A and intrathecal baclofen (ITB), as they are high-cost interventions and sufficient clinical evidence has been identified to allow for modelling. ITB and BoNT-A are used at different lines of therapy – BoNT-A may be used first line in people with focal spasticity; ITB is only used when other treatments have not worked – as a result separate analyses have been undertaken (ITB modelling work reported in Evidence Review P).

The incidence of post-stroke spasticity has been estimated at between 17% and 43% (17,000 to 43,000 people each year). The committee stated that people with mild post-stroke spasticity (PSS) who can recover reasonably well in the year following a stroke will not require these interventions. Some people may require interventions on a long-term basis. Treating spasticity aims to improve physical function and pain which may result in improved health-related quality of life and so increased QALYs. Furthermore, the committee noted that appropriate treatment of spasticity could have downstream cost savings for example by improving people's ability to care for themselves.

BoNT-A, as well as oral baclofen, were noted as conventional treatment options for those experiencing more moderate-severe PSS. BoNT-A is indicated for disability of the hand, wrist, foot and ankle due to upper or lower limb spasticity associated with stroke (specialist use only). Although BoNT-A is used currently in people with stroke, it is fairly high cost and the published cost effectiveness evidence was mixed with some studies finding it cost effective and others not (five cost utility analyses, reported in Evidence Review P).

Of the five health economic analyses were included in the review for BoNT-A, the first was a cost utility analysis (CUA) comparing Dysport to usual care for upper limb spasticity (Shackley 2012)[24] and found that over a 3-month time horizon, Dysport was not cost effective (ICER £93,000 per QALY). The second was a Scottish CUA comparing BOTOX to usual care in upper limb spasticity (Doan 2013)[5] and found that BOTOX was cost effective in one scenario (ICER £10,271 per QALY) where some of the health care resource use from another trial (BoTULS) was utilised and not cost effective when this was excluded (£27,134 per QALY). A third CUA comparing limited injection cycles of Xeomin (4 cycles) to unlimited cycles of Xeomin (Makino 2019)[13] in upper limb spasticity found unlimited cycles to not be cost-effective compared to limited cycles (ICER £28,457 per QALY). The fourth CUA compared BOTOX to Dysport in upper and lower limb spasticity and found Dysport dominated BOTOX in both populations (Danchenko 2022)[4]. The final analysis (Lindsay 2022)[12] was a cost effectiveness analysis comparing early treatment with BOTOX to usual care in upper limb spasticity and found that the cost savings and mean differences of the BI and ARAT score at 6 months were not statistically significant between study groups but a cost savings of £1,481 (BOTOX versus usual care) for the treatment of contractures was statistically significant.

Finally, the committee indicated that although it is already used in some stroke patients, they considered that a recommendation would result in increased use that could result in a significant resource impact.

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken where quality-adjusted life years (QALYs) and costs over a 1-year horizon from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting.[16] Due to the short time horizon, discounting was not required for the 12 week and 1 year analyses. Discounting at 3.5% for costs and health effects was applied for the 2-year analysis. An incremental analysis was undertaken.

2.1.1 Comparators

The following comparators were included in the analysis:

- OnaBoNT-A (BOTOX®)
- AboBoNT-A (Dysport®)
- IncoBoNT-A (Xeomin®)
- Usual care

The dosing reported in the clinical trials informing the model was used to cost the different BoNT-A drugs (see section 2.3.6.1 which details doses and costs).

2.1.2 Population

The population of the analysis was adults with post-stroke focal spasticity. Lower and upper limb focal spasticity were sub-grouped due to heterogeneity in the clinical review. The same approach was deemed appropriate in the health economic modelling, particularly as doses are different. Xeomin is not licensed for use in lower limb spasticity and so will not be a comparator in the lower limb model population. Of note, clinical evidence reporting outcomes that can inform the economic model is not available for all drugs for all indications (see summary of evidence below). As a result, the comparators included by type of focal spasticity were:

Lower limb spasticity:

1. Usual care
2. OnaBoNT-A (BOTOX®)

Upper limb spasticity:

1. Usual care
2. AboBoNT-A (Dysport®)
3. IncoBoNT-A (Xeomin®)

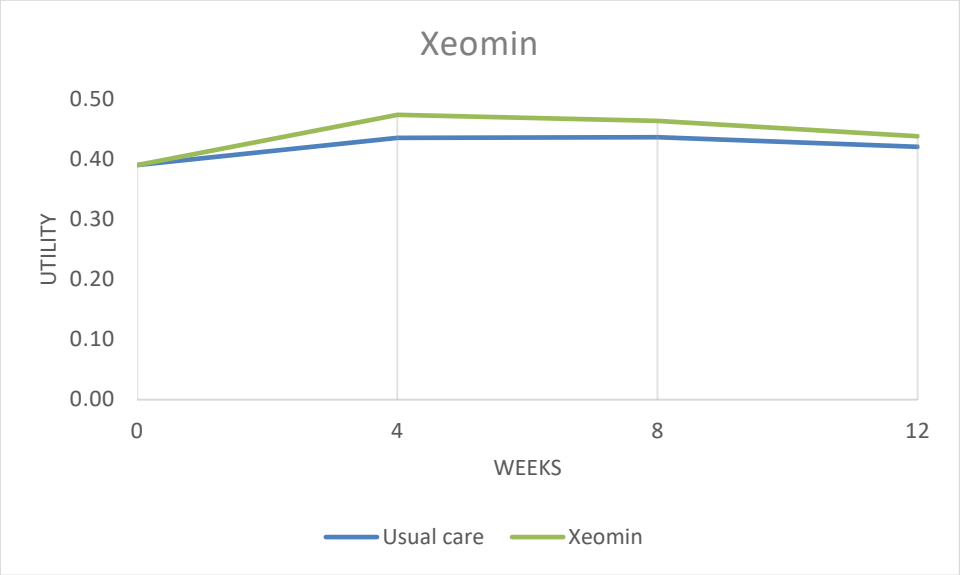
2.1.3 Time horizon

The model explored a 12 week, 1- and 2-year time horizon. The rationale for not including a lifetime horizon was that there is no evidence to suggest spasticity treatments would impact mortality. Furthermore, based on assessment of need, the literature suggested that most people received up to 4 injection cycles, approximately every 12 weeks and the number of patients requiring additional cycles progressively decreases (Turner Stokes 2021, Shaw 2010).[25, 29] Therefore, a 1-year time horizon was deemed sufficient to capture the impact of repeat injections of BoNT-A. A sensitivity analysis was conducted exploring a longer 2-year horizon (see 'Uncertainty' section below).

2.2 Approach to modelling

QALYs were estimated using Modified Ashworth Scale (MAS) responder data from the clinical review. The studies defined a MAS responder as a ≥1 point reduction in MAS, as this is considered statistically meaningful. Three RCTs were identified in the systematic review of the literature reporting MAS responder data, one for each drug.[6, 8, 33] The MAS responder data was reported at multiple time points thus allowing for QALYs over the trial period to be estimated using an area under the curve approach and applying 'responder' and 'non-responder' EQ-5D values, as done in one of the published cost utility analyses, Makino 2019.[13]

The area under the curve approach is illustrated for Xeomin below. The utility at each timepoint for Xeomin and Usual Care was calculated by multiplying the proportion of responders and non-responders by their respective utilities. The area below each line represents the QALYs over the trial period.



Several scenarios were explored whereby the time horizon was extend to 1 year and 2 years to account for repeat injections of BoNT-A. Repeat injections occur at a minimum of 12-week intervals. Some studies suggest a longer interval between injections however the evidence for this was limited and primarily observational,[29] therefore in this economic analysis only a 12-week interval was explored. The total number of injections in a year was assumed to be 4 and the proportion receiving repeat injections progressively decreased. This was based on observational and UK RCT evidence (Turner Stokes 2021, Shaw 2010).[25, 29] Further detail provided in the section on 'baseline probabilities'. A longer time horizon of 2 years was explored, with up to 8 injections received.

For repeat injections, it is assumed the QALY gain after a repeat injection will be the same as the QALY gain after the first injection, as the responders will continue to respond, and non-responders will remain non-responders. The costs however will decrease if fewer people receive repeat injections over time.

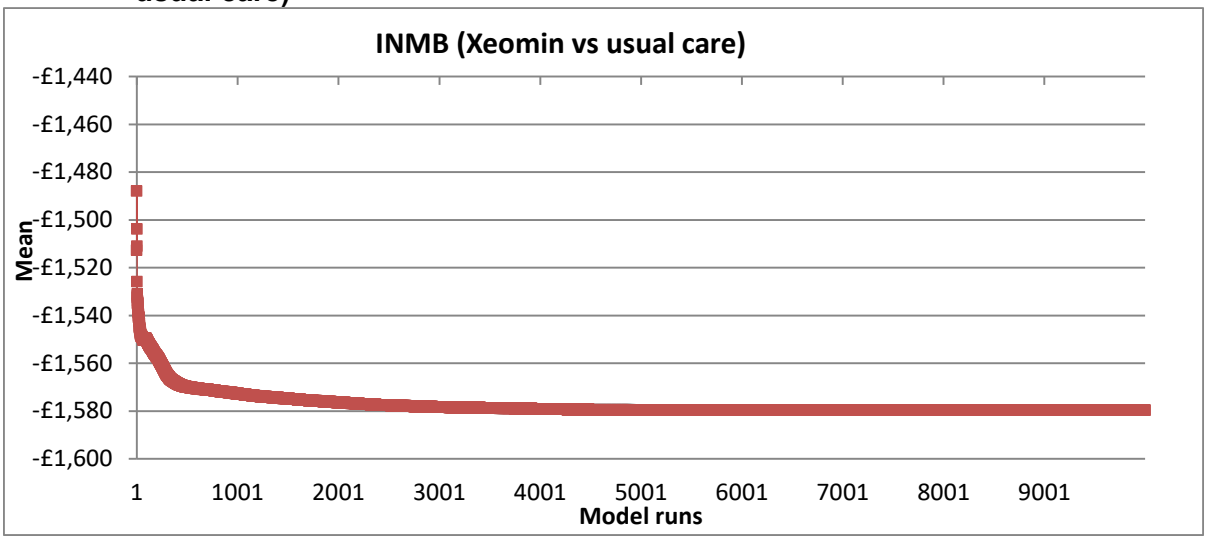
The costs of administration and the drugs are included in this analysis. The impact of BoNT-A on downstream costs were considered uncertain and therefore a threshold analysis was conducted to estimate magnitude of savings needed for BoNT-A to be cost-effective.

2.2.11 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for a number of model input parameters. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run 3,000 times for each analysis and results were summarised.

When running the probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis we checked for convergence in the incremental costs, QALYs and net monetary benefit at a threshold of £20,000 per QALY gained for Xeomin versus usual care over a 1-year time horizon, using the proportion of repeat injections from Shaw 2010. This was done by plotting the number of runs against the mean outcome at that point (see example in Figure 1) for the base-case analysis. Convergence was assessed visually and all had stabilised before 3,000 runs.

Figure 1: Checking for convergence: Incremental net monetary benefit (Xeomin vs usual care)



Abbreviations: INMB = incremental net monetary benefit.

The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Proportion of responders in placebo arms	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: • Alpha = (number of people responding) • Beta = (number of people) − (number of people responding)
Proportion of people	Beta	Bounded between 0 and 1. As the sample size and the

Parameter	Type of distribution	Properties of distribution
having a repeat injection		number of events were specified alpha and beta values were calculated as follows: • Alpha = (number of people having a repeat) • Beta = (number of people having previously had an injection) − (number of people having a repeat) These alpha and beta values ensure sampling is from the proportion of those having had a previous repeat injection, to ensure that the probabilities of repeats are always in descending order. The probabilistic value generated is then transformed back into a proportion of the whole population.
Mean difference in proportion of responders between BoNT-A and placebo	Normal	Unbounded. Derived from mean difference and its standard error. The standard error was calculated as follows, assuming the CI were calculated using the t-distribution given the small sample size: • SE = upper 95% CI − lower 95% CI/(2×TINV(0.025,total number of people-1)
Utilities	Beta	Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments. Standard error was calculated as follows: • SE = upper 95% CI − lower 95% CI/(2×NORMINV(0.975) Alpha and Beta values were calculated as follows: • Alpha = mean2×[(1−mean)/SE2]−mean • Beta = alpha×[(1−mean)/mean]

Abbreviations: 95% CI = 95% confidence interval; SE = standard error; SMR = standardised mortality ratio.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- the cost of BoNT-A and administration (these are list prices from BNF and NHS reference costs respectively, which represent national costs and not deemed to be uncertain).

In addition, various scenario sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 2.5 Sensitivity analyses.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the within trial period analysis, 1-year and 2-year analyses is provided in Table 2 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 2: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution

Input	Data	Source	Probability distribution
Comparators	Upper limb • Xeomin 400U • Dysport 500U • Dysport 1000U • Usual care (using placebo data) Lower limb • BOTOX 300U • Usual care (using placebo data)	Elovic 2016,[6] Gracies 2015[8] and Wein 2018[33]	n/a
Population	Adults with post stroke upper limb spasticity Adults with post stroke lower limb spasticity	Elovic 2016,[6] Gracies 2015[8] and Wein 2018[33]	n/a
Perspective	UK NHS & PSS	NICE reference case[16]	n/a
Time horizon	12 weeks, 1 year and 2 years.	12 week: Elovic 2016,[6] Gracies 2015[8] and Wein 2018[33] 1/2 years: Shaw 2010,[25] extrapolation and assumptions.	n/a
Discount rate	For 2-year analysis only: Costs: 3.5% Outcomes: 3.5%	NICE reference case[16]	n/a
Baseline probabilities			
Proportion of MAS responders in placebo arm – Xeomin study	0 weeks: 0% 4 weeks: 37.5% 8 weeks: 38.6% 12 weeks: 28%	Elovic 2016,[6]	Beta distribution alpha=33; beta=55 alpha=34; beta=54 alpha=22; beta=66
Proportion of MAS responders in placebo arm – Dysport study	0 weeks: 0% 4 weeks: 23% 12 weeks: 14% 16 weeks: 4% 20 weeks: 0%	Gracies 2015[8]	Beta distribution alpha=18; beta=61 alpha=11; beta=68 alpha=3; beta=76
Proportion of MAS responders in placebo arm – BOTOX study	0 weeks: 0% 2 weeks: 32% 4 weeks: 39% 6 weeks: 39% 8 weeks: 40% 12 weeks: 23%	Wein 2018[33]	Beta distribution alpha=76; beta=159 alpha=91; beta=144 alpha=92; beta=143 alpha=93; beta=142 alpha=54; beta=181
Relative treatment effects			
Mean difference in proportion of MAS responders: Xeomin versus placebo (SE)	0 weeks: 0% 4 weeks: 32% (5%) 8 weeks: 22% (6%) 12 weeks: 15% (5%)	Elovic 2016,[6]	Normal distribution
Mean difference in	0 weeks: 0%	Gracies 2015[8]	Normal distribution

Input	Data	Source	Probability distribution
proportion of MAS responders: Dysport 500U versus placebo (SE)	4 weeks: 51% (6%) 12 weeks: 29% (6%) 16 weeks: 15% (4%) 20 weeks: 10% (3%)		
Mean difference in proportion of MAS responders: Dysport 1000U versus placebo (SE)	0 weeks: 0% 4 weeks: 56% (6%) 12 weeks: 34% (6%) 16 weeks: 23% (5%) 20 weeks: 10% (3%)	Gracies 2015[8]	Normal distribution
Mean difference in proportion of MAS responders: BOTOX versus placebo (SE)	0 weeks: 0% 2 weeks: 13% (4%) 4 weeks: 13% (4%) 6 weeks: 14% (4%) 8 weeks: 9% (4%) 12 weeks: 9%	Wein 2018[33]	Normal distribution
Repeat injections			
Time between repeat injections	12 weeks	Shaw 2010[25]	n/a
Proportion receiving repeat injections 1st year	2nd injection: 67.7% 3rd injection: 61% 4th injection: 51.4%	Shaw 2010[25]	Beta distribution alpha=70; beta=33 alpha=63; beta=7 alpha=53; beta=10
Scenario analyses: Repeat injections			
Proportion receiving repeat injections 2nd year (extrapolation)	5th injection: 46.5% 6th injection: 42.7% 7th injection: 39.7% 8th injection: 37.3%	Extrapolation of Shaw 2010, [25] using a power trendline.	Beta distribution alpha=48; beta=5 alpha=44; beta=4 alpha=41; beta=3 alpha=38; beta=2
Proportion receiving repeat injections 2nd year (assumption = 4th injection)	5th injection: 51.4% 6th injection: 51.4% 7th injection: 51.4% 8th injection: 51.4%	Assumption based on Shaw 2010[25]	Beta distribution alpha=53; beta=10
All receiving repeat injections 1st and 2nd year	Each injection (2nd to 8th): 100%	Assumption	fixed
Health-related quality of life (utilities)			
Responder utility (SE)	0.51 (0.02)	Makino 2019[13]	Beta distribution alpha=305; beta=294
Non-responder utility (SE)	0.39 (0.02)	Makino 2019[13]	Beta distribution alpha=222; beta=348
Costs			
Xeomin 400U	£519.60	BNF online, accessed November 2022[2]	n/a
Dysport 500U / 1000U	£154.00 / £308.00	BNF online, accessed November 2022[2]	n/a
BOTOX 300U	£414.60	BNF online, accessed November 2022[2]	n/a
First appointment for administration	£244	Neurology, Consultant-led Multiprofessional	n/a

Input	Data	Source	Probability distribution
of BoNT-A		Non-Admitted Face-to-Face Attendance, First. NHS reference costs 2019/2020[20]	
Subsequent appointment for repeat injection BoNT-A	£187	Neurology, Consultant-led Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up. NHS reference costs 2019/2020[20]	n/a

Abbreviations: BoNT-A = botulinum toxin A; MAS = Modified Ashworth Scale; n/a = not applicable; SE = standard error, U = units.

2.3.2 Baseline probabilities

Proportion of MAS responders usual care

MAS responder data was used as the treatment effect in this analysis, this was included by applying the mean difference in MAS responders for BoNT-A compared to placebo onto the placebo proportion of MAS responders. The proportion of MAS responders in the placebo arms of the trials were used for the usual care comparator in these analyses. These are reported in below (Table 3), along with the sample size, probability distribution and alpha and beta.

Table 3: Proportion of MAS responders in placebo arm

Drug (Study)	% MAS responders placebo	Sample size	Probability distribution
Xeomin (Elovic 2016)[6]	0 weeks: 0% 4 weeks: 37.5% 8 weeks: 38.6% 12 weeks: 28%	N=88	Beta distribution alpha=33; beta=55 alpha=34; beta=54 alpha=22; beta=66
Dysport (Gracies 2015)[8]	0 weeks: 0% 4 weeks: 23% 12 weeks: 14% 16 weeks: 4% 20 weeks: 0%	N=79	Beta distribution alpha=18; beta=61 alpha=11; beta=68 alpha=3; beta=76
BOTOX (Wein 2018)[33]	0 weeks: 0% 2 weeks: 32% 4 weeks: 39% 6 weeks: 39% 8 weeks: 40% 12 weeks: 23%	N=235	Beta distribution alpha=76; beta=159 alpha=91; beta=144 alpha=92; beta=143 alpha=93; beta=142 alpha=54; beta=181

Abbreviations: MAS = modified Ashworth scale.

Proportion receiving repeat injections

Only one of the three RCTs informing the MAS responder data included repeat injections, Wein et al 2018.[33] This was part of an open label phase of the trial where all participants were given 3-monthly repeat injections, rather than providing repeat injections based on an assessment of need or response. As a result, alternative data sources were considered to inform what proportion would have repeat injections and how many on average they would receive. Other sources included other RCTs in clinical review; summary of product characteristics and real-world evidence/observational data.

Shaw 2010 (BoTULS),[25] a UK based RCT, reported that at 3, 6 and 9 months, further injections were received by 67.7%, 61.0% and 51.4% intervention group participants, respectively.

Summary of product characteristics for all three formulations report that repeat treatment should be administered no more frequently than every 12 weeks.

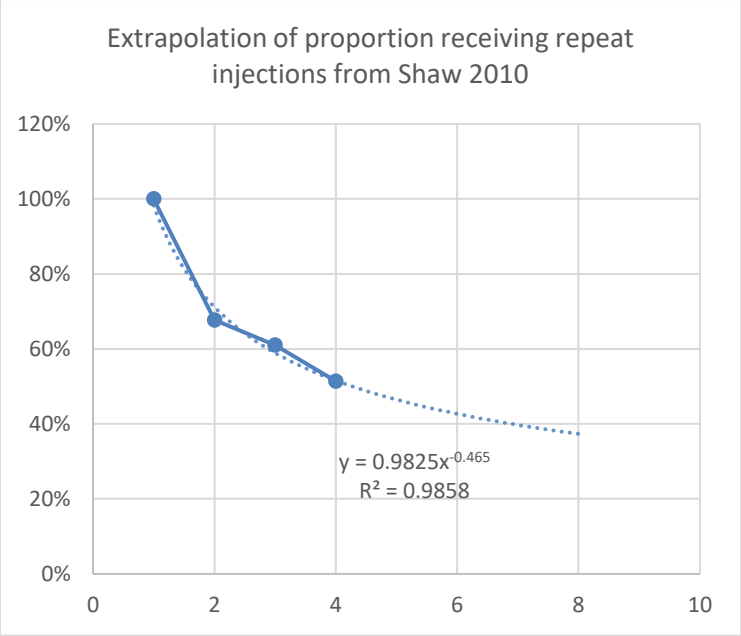
Real world evidence identified included ULIS-II (Turner-Stokes 2013)[28] a large, international, prospective cohort study which reported the median number of BoNT-A injections previously received by the participants was 4 (IQR 1–8; range 1–45). In this cohort, at visit 2, the median (range) follow-up time was 14 (2.6–32.3) weeks, and further injection was planned in 361 (79.2%) participants. ULIS-III (Turner-Stokes 2021)[29] reported that the number of treatment cycles given during the follow-up period depended on the patient's condition, their treatment goals and local practice and participants underwent a median (range) of 4 (1–9) BoNT-A injection cycles during the 2-year period. The number of participants requiring higher numbers of cycles progressively decreased. The study noted that a 3-month interval between injections was permitted but not routine practice in this cohort. It should be noted, however, that the majority of patients included in the study were receiving Dysport, which was confirmed to have a longer injection interval than the other products, so its predominant use could therefore have skewed the overall number of injection cycles down (i.e. fewer injections) than might have been seen with more equal sample sizes for BOTOX and Xeomin. The longer duration observed between Dysport injections was not explored quantitively in the model given the evidence is observational and was not appraised as part of the clinical review. Increased duration between injections could reduce costs and increase QALYs, this is discussed qualitatively as an additional consideration in the discussion section.

Based on this information, one scenario was explored where, over a 1-year time horizon, people would receive up to 4 cycles of BoNT-A injections every 12 weeks and that the proportions having the repeat cycles would decrease and be taken from BoTULS trial (Shaw 2010).[25] Some committee members thought that this may be underestimating the proportion of people receiving repeat injections in current practice and therefore an analysis was conducted where all people would continue to receive repeats over the course of 1 year.

A 2-year time horizon was also explored in three separate analyses:

1. All those in the BoNT-A group continued to receive repeats.
2. Proportion receiving repeat injections from the BoTULS trial data was plotted and extrapolated using a power trendline in Excel to estimate the proportion receiving repeats in year 2 (see Figure 2). The LINEST function was used to generate the power trendline equation values.
3. Proportion receiving injections in year 2 (injections 5-8) is the same as proportion receiving last injection in BoTULS trial data (injection 4).

Figure 2: Extrapolation of BoTULS (Shaw 2010) data on repeats



Source: Shaw 2010[25]

A summary of these inputs, along with the sample size, probability distribution and alpha and beta where applicable is provided in Table 4 below.

Table 4: Data on repeat injections

Scenario and source	% receiving repeat injections	Sample size	Probability distribution
Proportion receiving repeat injections 1st year (Shaw 2010)[25]	2nd injection: 67.7% 3rd injection: 61% 4th injection: 51.4%	N=103	Beta distribution (a) alpha=70; beta=33 alpha=63; beta=7 alpha=53; beta=10
Proportion receiving repeat injections 2nd year (Shaw 2010[25] with extrapolation)	5th injection: 46.5% 6th injection: 42.7% 7th injection: 39.7% 8th injection: 37.3%	Assume n=103	Beta distribution (a) alpha=48; beta=5 alpha=44; beta=4 alpha=41; beta=3 alpha=38; beta=2
Proportion receiving repeat injections 2nd year (Assumption 5th-8th = 4th injection)	5th injection: 51.4% 6th injection: 51.4% 7th injection: 51.4% 8th injection: 51.4%	Assume n=103	Beta distribution (a) alpha=53; beta=10 (for all)
All receiving repeat injections 1st and 2nd year	Each injection (2nd to 8th): 100%	n/a	fixed

Abbreviations: n/a = not applicable.

(a) These alpha and beta values ensure sampling is from the proportion of those having had a previous repeat injection, to ensure that the probabilities of repeats are always in descending order. The probabilistic value generated is then transformed back into a proportion of the whole population.

2.3.3 Relative treatment effects

A detailed discussion of the different clinical outcome data available from this review question and how it was decided upon which evidence to use in this analysis is outlined below.

Direct EQ-5D from the clinical review would be the preferred outcome to include in a health economic analysis. EQ-5D data was only reported in two RCTs of BoNT-A (Shaw 2010[25] and Wallace 2020[31]). Shaw 2010[25] is an RCT of Dysport (500U) for upper limb spasticity used in one of the published CUA summarised in the evidence review (Shackley 2012)[24] and the second RCT, Wallace 2020[31], is a study of BOTOX for upper limb spasticity (n=28, dose=100U). The latter study reported a harm in terms of EQ-5D but the dose of BOTOX was low and the study was in a very small sample of chronic patients.

Given the limited EQ-5D data reported in the included clinical studies, other clinical outcomes were considered in order to maximise the data that could be incorporated into the economic analysis. Outcomes considered to enable health economic modelling included the Barthel Index, Modified Ashworth Scale, Disability Assessment Scale or Numeric Rating Scale for pain. These were each considered in turn and a summary is provided below.

Barthel Index (BI) consists of 10 items that measure a person's daily functioning particularly activities of daily living and mobility. This outcome was reported in three RCTs of BoNT-A (Rosales 2012, Turcu-Stiolica 2021, Tao 2015)[22, 26, 27] and can be mapped to EQ-5D, as done in the stroke intensity model (Evidence Review E – Intensity Model) using the mapping function reported in Van Exel 2004[30]. This approach was considered to not be appropriate as BI does not capture pain, an important outcome for spasticity, and therefore this mapping is likely to underestimate QALY gain.

Disability Assessment Scale (DAS) was used in the published CUA by Doan 2013,[5] whereby a utility was assigned to each 'disability state' in the model. Therefore, to replicate this model approach, data on the DAS domain distribution is required. Only two RCTs included in the clinical review reported this; Brashear 2002[3] which was the RCT that provided the clinical evidence for the existing CUA by Doan 2013,[5] and the other is Gracies 2015[8] (Dysport). Given the limited new evidence, alternative outcome measures were considered to enable modelling of BoNT-A.

Numeric Rating Scale (NRS) for pain was the clinical outcome that was mapped to utilities in the NG144 Sativex spasticity modelling.[15] It was not considered a viable modelling approach as only a single RCT reported this outcome (Esquenazi 2019)[7] and only reported change scores at 6 weeks follow up.

Modified Ashworth Scale (MAS) measures resistance during passive soft tissue stretching and is used as a measure of spasticity. MAS is frequently reported in the RCTs, however most trials report mean MAS data as opposed to the proportion of responders, where responders are defined as those with a reduction in MAS score of 1 or more. As mentioned in the modelling approach section, an existing CUA of BoNT-A by Makino 2019[13] utilised EQ-5D values by MAS responder status from a post-hoc analysis of Kanovsky 2009[11] (RCT included in clinical review). These EQ-5D values by responder status could be applied in this model if responder analysis data is available from the clinical evidence.

Of note, mapping MAS to EQ-5D was not an option. One conference abstract reporting mapping doesn't provide actual values and discourages mapping from MAS to EQ-5D.[9]

Fifty RCTs reporting MAS mean data were available however only three RCTs reported responder data. Dichotomising the continuous data is an approach that has been used in other NICE health economic models, such as NG144[15] Sativex Chronic Pain model and was considered here. One of the three RCTs with responder analysis reported the actual mean MAS change distribution and from this it was possible to see that the data was not normally distributed (Wein 2018).[33] The NG144[15] Sativex Chronic Pain economic model states the need for data to be normally distributed for dichotomising continuous outcomes, as does a methods paper by Peacock 2012.[21] As a result, it was considered not feasible to dichotomise the continuous MAS data for the purposes of modelling. Of note, a similar limitation was encountered in the NG144[15] Sativex MS spasticity model. Therefore, only three RCTs with MAS responder data are useable for modelling, these were:

Upper limb spasticity:

- Dysport versus placebo (Gracies 2015,[8] n=243, dose=500/1000U)
- Xeomin versus placebo (Elovic 2016,[6] n=259, dose 400U)

Lower limb spasticity:

- BOTOX versus placebo (Wein 2018,[33] n=468, dose 300U)

The advantage of using MAS responder data for modelling is that the trials are large multicentre trials, and it would allow for comparison with one of the existing BoNT-A CUA. There are some concerns with the EQ-5D data being used that are detailed in the utilities section below. Despite these concerns, modelling using MAS was considered the best approach to explore uncertainty in cost effectiveness as it makes use of additional clinical evidence not used in current CUA.

Summarised in Table 5 are the proportions of MAS responders for each BoNT-A at the various follow up points. This data, along with the placebo data was entered into EPPI to calculate the mean difference for BoNT-A versus placebo for each timepoint, as well as 95% confidence intervals. This data is also included in Table 5, along with the probability distribution and calculated standard error used in the probabilistic analysis.

Table 5: Mean difference in proportion of MAS responders

Drug (Study)	% MAS responders BoNT-A	Sample size	Mean difference BoNT-A vs placebo (95%CI)	Probability distribution
Xeomin (Elovic 2016)[6]	0 weeks: 0% 4 weeks: 69.6% 8 weeks: 60.8% 12 weeks: 39.8%	N=171	0 weeks: 0% 4 weeks: 32% (20%,44%) 8 weeks: 22% (10%, 35%) 12 weeks: 15% (3%, 26%)	Normal distribution SE=5% SE=6% SE=5%
Dysport 500U (Gracies 2015)[8]	0 weeks: 0% 4 weeks: 74% 12 weeks: 43% 16 weeks: 19% 20 weeks: 10%	N=80	0 weeks: 0% 4 weeks: 51% (38%, 64%) 12 weeks: 29% (15%, 42%) 16 weeks: 15% (5%, 24%) 20 weeks: 10% (3%, 17%)	Normal distribution SE=6% SE=6% SE=4% SE=3%
Dysport 1000U (Gracies 2015)[8]	0 weeks: 0% 4 weeks: 79% 12 weeks: 48% 16 weeks: 27% 20 weeks: 10%	N=79	0 weeks: 0% 4 weeks: 56% (43%, 69%) 12 weeks: 34% (21%, 48%) 16 weeks: 23% (12%, 33%) 20 weeks: 10% (3%, 17%)	Normal distribution SE=6% SE=6% SE=5% SE=3%
BOTOX (Wein 2018)[33]	0 weeks: 0% 2 weeks: 45% 4 weeks: 52% 6 weeks: 53% 8 weeks: 49% 12 weeks: 32%	N=233	0 weeks: 0% 2 weeks: 13% (4%, 21%) 4 weeks: 13% (4%, 22%) 6 weeks: 14% (5%, 23%) 8 weeks: 9% (0%, 18%) 12 weeks: 9% (1%, 17%)	Normal distribution SE=4% SE=4% SE=4% SE=4%

Abbreviations: 95%CI = 95% confidence intervals; BoNT-A = botulinum toxin type A; MAS = modified Ashworth scale; SE = standard error.

2.34 Life expectancy

There was no evidence to suggest spasticity treatments would impact mortality and therefore a treatment effect on mortality was not included in the analysis. This reflects the approach

taken in prior health economic analyses of BoNT-A identified in the health economic review. Due to the short time horizon all-cause mortality was not included in this analysis.

2.3.5 Utilities

Utilities were taken from the Makino 2019[13] cost utility analysis, where patients in the response health state accrued a utility value of 0.51 (SD 0.32, 95%CI 0.47, 0.55), while those not in response accrued a utility value of 0.39 (SD 0.24), which was the EQ-5D utility value of the population at baseline. These responder and non-responder EQ-5D estimates were taken from a post-hoc analysis of Kanovsky 2009,[11] an RCT included in clinical review. The EQ-5D data was not reported in the RCT publication and was only available in Makino 2019.[13]

Some concerns have been noted with using this EQ-5D. Firstly, the EQ-5D data is provided by responder status not by randomised group and it is unclear if any adjustments made to account for potential confounders. EQ-5D questionnaires collection times were not reported, and therefore it is not clear if these were done when the effects of treatment are expected to peak (approximately 4 weeks) or if they were done once the effects had started to diminish over time. According to Makino 2019, Australian preference weights were applied. Finally, Kanovsky 2009[11] was an RCT in upper limb spasticity and using 400U Xeomin, therefore the EQ-5D data may be less applicable to lower limb spasticity benefits or to other BoNT-A types or doses.

For the probabilistic analysis, a beta distribution was applied to these utilities. The sample number was not reported and so the standard error could not be estimated from the standard deviation. For the responder utility, the 95% confidence intervals were reported allowing for the standard error to be estimated. The standard error for non-responder utility was assumed to be the same as that of responders.

2.3.6 Resource use and costs

2.3.6.1 Drugs

Drug costs were taken from the British National Formulary[2] and doses taken from the mean doses reported in the trials that reported the MAS responder data (Table 6). As the doses reported in the trials were a single full vial or multiple full vials, the unit costs did not need to account for vial wastage in the calculation. The same dose and drug were assumed to be used for a repeat injection as was used for first injections.

Table 6: BoNT-A drug costs

Drug	Cost per vial	Unit cost
Xeomin	50U: £72.00 100U: £129.90 200U: £259.80	400U: £519.60
Dysport	300U: £92.40 500U: £154.00	500U: £154.00 1000U: £308.00
BOTOX	50U: £77.50 100U: £138.20 200U: £276.40	300U: £414.60

Source: BNF online[2], Elovic 2016,[6] Gracies 2015,[8] Wein 2018[33]

2.3.6.2 Administration

Existing health economic analyses as well as NHS reference costs were considered when costing BoNT-A administration.

The existing cost utility analyses included the following unit costs and assumptions for BoNT-A administration:

- Shaw 2010/Shackley 2012:[24, 25] one hour of therapist time, £40 per session (PSSRU unit cost 2007).
- Doan 2013:[5] did not explicitly cost administration but assumed a specialist office visit for BoNT-A every 12 weeks (approximately 4 a year) and two specialist office visits for the control arm, £128 a visit (NHS reference costs 2008-2009)
- Makino 2019:[13] specialist consultation and other services (injection, neuromuscular stimulation and ultrasound), £145 per session (Australian Medicare Benefits Scheme claims data, 2017, converted to 2017 UK £)
- Danchenko 2022:[4] an outpatient neurology follow-up attendance, £116 (NHS National Tariff 2019-2020)
- Lindsay 2022:[12] one hour of therapist (band 6) time, £45 per session (PSSRU 2019)

In NICE TA260,[14] BoNT-A for use in migraine, the administration cost for BoNT-A was costed as 30 mins of consultant time. The Evidence Review Group suggested this was optimistic and up to one hour may be required. This approach however would not capture the cost of consumables required for administration or the cost of equipment needed for imaging.

The Royal College of Physicians (RCP) botulinum toxin guidelines[23] which suggest several resource use points when administering BoNT-A for spasticity, these include:

- Pre-injection consultation
- Injection, including a localisation of injection site: using EMG or nerve/muscle stimulator or imaging (CT/Ultrasound) as needed
- Follow up assessment required after treatment

After careful consideration of the above information, the committee agreed to include NHS reference costs[19] for 'consultant led multidisciplinary team face to face neurology attendances' to account for the administration cost. It was considered that this cost would incorporate both the time of the injector and any imaging required. From their experience the injector would either be a consultant or a non-medical injection (physiotherapist band 6 or above) within a consultant-led multidisciplinary team. To account for any initial assessment required prior to commencing BoNT-A, it was assumed the first administration attendance would take longer than repeat injections. Therefore, it was assumed the first injection would be a 'first' attendance and repeat injections would be 'follow-up' attendances. The committee noted that although as stated by the RCP guidance a follow up appointment at 4 weeks to check response would be best practice, this is not done in current practice. In current practice, people are asked about their response 12 weeks later, when they attend for a repeat injection. Therefore, in this analysis to reflect current practice, it is assumed the follow up to check response is done as part of the repeat administration, not in a separate appointment at 4 weeks.

The unit costs used are summarised in Table 7 below.

Table 7: BoNT-A administration costs

Resource use	Unit cost	Source	Probability distribution
First appointment for administration of BoNT-A	£244	Neurology, Consultant-led Multiprofessional Non-Admitted Face-to-Face Attendance, First. NHS reference costs 2019/2020[19]	Fixed
Subsequent appointment for repeat injection BoNT-A	£187	Neurology, Consultant-led Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up. NHS reference costs 2019/2020[19]	Fixed

It was noted by the committee that using these costs may be an underestimate of the true cost of administration for more dependent people as they would require home treatment or an ambulance to attend a hospital appointment and possibly a longer outpatient appointment to account for more time for dressing or use of a hoist. This will be taken account of qualitatively when reviewing the results.

Following discussion with the committee it was unclear whether these attendances were over and above standard spasticity care (not BoNT-A) in current practice. In the base case analysis, it is assumed that those receiving usual care or those who were not receiving repeat injections would incur no outpatient attendances for their spasticity, thus assuming that the BoNT-A administration attendances were over and above usual care. This was explored in a sensitivity analysis whereby those in the usual care arm and those who no longer receive repeat injections would have twice yearly follow up attendances to manage their spasticity (£187 each). This sensitivity analysis reflects the assumptions in Doan 2013.[5]

2.3.6 Downstream costs

The downstream costs following treatment with BoNT-A were considered to be unclear. The committee thought that for those with high levels of dependency, spasticity management with BoNT-A would be focused on easing pain rather than significant improvements in mobility or activities of daily living and therefore treatment was unlikely to impact the cost of the total package of care they receive. For others, if treatment is successful there is the potential that this will increase their ability to engage in rehabilitation, thus increasing rehabilitation costs but also increasing QALYs. Neither of which we have evidence to quantify.

Only two included RCTs in the clinical review reports health care resource use BoTULS (Shaw 2010)[25] and Lindsay 2022.[12] In BoTULS when the 3-month resource use was included in the Shackley 2012[24] CUA, it resulted in higher costs for the BoNT-A group compared to usual care, even when cost of treatment was excluded. In Lindsay 2022,[12] the study reports no difference in health care resource use for early BoNT-A versus placebo other than a reduction in costs associated with contractures. Given that the RCT evidence informing this analysis is not reporting on early use of BoNT-A it was not considered appropriate to include savings associated with contractures into the analysis.

Other evidence on resource use was identified in the literature but these were based on Delphi panels or expert opinion surveys/questionnaires in industry funded publications and conference abstracts and therefore were not considered to be robust sources of evidence (Johnston 2020, Ward 2005 and Abogunrin 2015).[1, 10, 32]

Due to challenges in accurately quantifying downstream costs, a threshold analysis was undertaken, to estimate the magnitude of downstream savings needed for BoNT-A to be cost-effective.

2.4 Computations

The model was constructed in Microsoft Excel 365®. The QALYs were calculated using an area under the curve for each comparator. Utilities were calculated by weighting for responders and non-responders. Area under the curve was calculated using the formula as follows:

$\text{QALY AUC} = \frac{1}{2}(utility\ n0 + utility\ n1) \times \frac{(n1 - n0)}{52}$	Where: *AUC* = Area under the curve *QALYs*=quality adjusted life years *n*=time (weeks)

This was done for each time point interval and the total QALYs was estimated by adding them together.

The total costs were also calculated over that time period for each comparator. All those in the BoNT-A comparators would receive a first injection which would include the drug cost and first neurology appointment for assessment and administration cost. For those receiving repeat injection, they would incur the drug cost again and a follow up neurology appointment cost for the administration cost. Those in the usual care arm would incur no costs in the base case.

In the 2-year time horizon analysis, QALYs were discounted to reflect time preference (discount rate 3.5%). QALYs during the first year were not discounted. The total discounted QALYs were the sum of the discounted QALYs per year. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$

Where:
r=discount rate per annum
n=time (years)

2.54 Sensitivity analyses

The following scenario analyses were undertaken to explore uncertainty in the model assumptions.

SA1: Model within trial period

Only the trial period (up to 12 weeks) data was utilised and therefore only a single BoNT-A injection cycle was administered.

SA2/3: 1 year horizon, all receive repeats +/- neurology attendances for usual care

A one-year time horizon was explored, where all those in the BoNT-A comparator received repeat injections (total 4 in one year) irrespective of an assessment of need or assessment of response. This was done without the usual care arm receiving twice annual follow up neurology consultant-led multidisciplinary attendances (SA2) and with them receiving these attendances (SA3).

SA4/5: 1 year horizon, Shaw/BoTULS data on repeat +/- neurology attendances for usual care / those not receiving repeat injections

A one-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[25] up to a total of 4 injection cycles in one year. This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA4) and with them receiving these attendances (SA5).

SA6/7: 2 year horizon, all receive repeats +/- neurology attendances for usual care / those not receiving repeat injections

A two-year time horizon was explored, where all those in the BoNT-A comparator received repeat injections (total 8 over two years) irrespective of an assessment of need or assessment of response. This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA6) and with them receiving these attendances (SA7).

SA8/9: 2 year horizon, Shaw/BoTULS data on repeat extrapolated +/- neurology attendances for usual care / those not receiving repeat injections

A two-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010)[25] for the first year and extrapolated for the second year using a trendline, up to a total of 8 injection cycles over two years. This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA8) and with them receiving these attendances (SA9).

SA10/11: 2 year horizon, Shaw/BoTULS data, injection 5-8 same as % at injection 4, +/- neurology attendances for usual care / those not receiving repeat injections

A two-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010)[25] for the first year and in the second year it was assumed the proportion receiving injections 5 to 8 was the same as the proportion receiving injection 4. This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA10) and with them receiving these attendances (SA11).

2.6 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the health economics team; this included systematic checking of the model calculations.

2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost effective if:
- ICER < Threshold

2.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[16-18] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

1

3 Results

SA1: Model within trial period

When only the trial period (up to 12 weeks) data was utilised and therefore only a single BoNT-A injection cycle was administered, none of the BoNT-A drugs were cost effective compared to usual care at a threshold of £20,000 per QALY (probability cost effective of 0%). The ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. When a threshold analysis was conducted to estimate the magnitude of downstream savings over the 12-week time horizon required for BoNT-A to be cost effective at £20,000 per QALY this was from £204 for Dysport (500U) to £650 for Xeomin. At a threshold of £30,000 per QALY the probability of Dysport (500U) being cost effective versus usual care was 8%. For the other drugs, was 0-1% versus usual care. Probabilistic results are summarised in Table 8. The probabilistic and deterministic results were very similar and the conclusions regarding overall cost effectiveness were there same. This was true for all analyses (SA1 to SA11), therefore only the probabilistic results were presented as they quantify uncertainty in the results.

Table 8: Probabilistic results SA1

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
SA1 Within trial results - 12 weeks (a)									
Xeomin	£764	0.104	£764	0.006	£134,404	£650	£593	0%	0%
UC	£0	0.098							
Dysport 500U	£398	0.104	£398	0.010	£41,110	£204	£108	0%	8%
UC	£0	0.094							
Dysport 1000U	£552	0.105	£552	0.011	£50,690	£334	£225	0%	1%
UC	£0	0.094							
BOTOX	£659	0.102	£659	0.003	£225,203	£600	£571	0%	0%
UC	£0	0.099							

Abbreviations: ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years; SA = scenario analysis; UC = usual care. Threshold analysis estimates the magnitude of downstream savings needed for BoNT-A to be cost-effective at different cost effectiveness thresholds.

(a) Each type of BoNT-A is compared to the usual care arm from its respective trial (Xeomin (Elovic 2016)[6], Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA2/3: 1 year horizon, all receive repeats +/- neurology attendances for usual care

When a one-year time horizon was explored, where all those in the BoNT-A comparator received repeat injections (total 4 in one year) irrespective of an assessment of need or assessment of response, none of the BoNT-A drugs were cost effective compared to usual care at a threshold of £20,000 per QALY. This was the case when the usual care arm did not or did receive twice annual follow up neurology consultant-led multidisciplinary attendances (SA2 & SA3).

As in SA1, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. The ICERs were lower for SA3, where the usual care arm had twice yearly follow-up attendances to manage their spasticity, however these remained above £20,000 per QALY. When a threshold analysis was conducted to estimate the magnitude of downstream savings over the 1-year time horizon required for BoNT-A to be cost effective at £20,000 per QALY this was lowest for Dysport (500U) in SA3: £273, and highest for Xeomin in SA2: £2,428. At a threshold of £20,000 per QALY the probability of Dysport 500U being cost effective versus usual care was 9% in SA3. For the other drugs, was 0% versus usual care. All probabilistic results are summarised in Table 9.

Table 9: Probabilistic results: SA2 and SA3

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
SA2 1 year horizon - all receive repeat + no attendances for UC (a)									
Xeomin	£2,883	0.415	£2,883	0.023	£126,673	£2,428	£2,201	0%	0%
UC	£0	0.393							
Dysport 500U	£1,421	0.417	£1,421	0.039	£36,511	£643	£253	0%	21%
UC	£0	0.378							
Dysport 1000U	£2,037	0.421	£2,037	0.043	£46,968	£1,170	£736	0%	2%
UC	£0	0.378							
BOTOX	£2,463	0.407	£2,463	0.012	£210,942	£2,230	£2,113	0%	0%
UC	£0	0.396							
SA3 1 year horizon - all receive repeat + attendances for UC (a)									
Xeomin	£2,883	0.415	£2,509	0.023	£110,359	£2,055	£1,827	0%	0%
UC	£374	0.393							
Dysport 500U	£1,421	0.417	£1,047	0.039	£27,068	£273	n/a	9%	64%

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
UC	£374	0.378							
Dysport 1000U	£2,037	0.421	£1,663	0.043	£38,516	£799	£368	0%	13%
UC	£374	0.378							
BOTOX	£2,463	0.407	£2,089	0.012	£179,604	£1,857	£1,740	0%	0%
UC	£374	0.396							

Abbreviations: ICER = incremental cost effectiveness ratio; n/a = not applicable; QALYs = quality adjusted life years; SA = scenario analysis; UC = usual care. Threshold analysis estimates the magnitude of downstream savings needed for BoNT-A to be cost-effective at different cost effectiveness thresholds.

(a) Each type of BoNT-A is compared to the usual care arm from its respective trial (Xeomin (Elovic 2016)[6], Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA4/5: 1 year horizon, Shaw/BoTULS data on repeat +/- neurology attendances for usual care / those not receiving repeat injections

When a 1-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[25] up to a total of 4 injection cycles in one year, only Dysport (500U) was cost-effective compared to usual care (ICER: £19,361 per QALY, probability cost effective 53%) in the analysis where the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances (SA5). All other BoNT-A were not cost effective compared to usual care at £20,000 per QALY.

As in SA1, SA2 and SA3, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. The ICERs were lower for SA5, where the usual care arm and those not receiving repeat injections had twice yearly follow up attendances to manage their spasticity when compared to SA4. When a threshold analysis was conducted to estimate the magnitude of downstream savings over the 1-year time horizon required for BoNT-A to be cost effective at £20,000 per QALY this was lowest for Dysport (500U) in SA4: £249, and highest for Xeomin in SA4: £1,586. All probabilistic results are summarised in Table 10.

Table 10: Probabilistic results: SA5 and SA5

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
SA4 1 year horizon - Shaw 2010 data on repeat + no attendances for UC/those not receiving repeats (a)									
Xeomin	£2,039	0.416	£2,039	0.023	£89,982	£1,586	£1,359	0%	0%
UC	£0	0.393							
Dysport 500U	£1,013	0.417	£1,013	0.039	£26,215	£240	n/a	13%	67%

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
UC	£0	0.378							
Dysport 1000U	£1,442	0.421	£1,442	0.044	£32,945	£566	£129	1%	34%
UC	£0	0.378							
BOTOX	£1,744	0.408	£1,744	0.012	£149,081	£1,510	£1,393	0%	0%
UC	£0	0.396							
SA5 1 year horizon - Shaw 2010 data on repeat + attendances for UC/non-responders (a)									
Xeomin	£2,149	0.415	£1,775	0.023	£78,081	£1,320	£1,093	0%	0%
UC	£374	0.393							
Dysport 500U	£1,125	0.417	£751	0.039	£19,361	n/a	n/a	53%	92%
UC	£374	0.378							
Dysport 1000U	£1,556	0.421	£1,182	0.043	£27,330	£317	n/a	8%	63%
UC	£374	0.378							
BOTOX	£1,855	0.407	£1,481	0.012	£126,592	£1,247	£1,130	0%	0%
UC	£374	0.396							

Abbreviations: ICER = incremental cost effectiveness ratio; n/a = not applicable; QALYs = quality adjusted life years; SA = scenario analysis; UC = usual care. Threshold analysis estimates the magnitude of downstream savings needed for BoNT-A to be cost-effective at different cost effectiveness thresholds.
(a) Each type of BoNT-A is compared to the usual care arm from its respective trial (Xeomin (Elovic 2016)[6], Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA6/7: 2-year horizon, all receive repeats +/- neurology attendances for usual care / those not receiving repeat injections

When a two-year time horizon was explored, where all those in the BoNT-A comparator received repeat injections (total 8 over two years) irrespective of an assessment of need or assessment of response, none of the BoNT-A drugs were cost effective compared to usual care at a threshold of £20,000 per QALY. This was the case when the usual care arm did not or did receive twice annual follow up neurology consultant-led multidisciplinary attendances (SA6 & SA7).

As in the other scenario analyses, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. The ICERs were lower for SA7, where the usual care arm had twice yearly follow-up attendances to manage their spasticity, however these remained above £20,000 per QALY. When a threshold analysis was conducted to estimate the magnitude of downstream savings over the 2-year time

horizon required for BoNT-A to be cost effective at £20,000 per QALY this was lowest for Dysport (500U) in SA7: £467, and highest for Xeomin in SA6: £4,717. At a threshold of £20,000 per QALY the probability of Dysport 500U being cost effective versus usual care was 12% in SA7. For the other drugs, was 0% versus usual care. All probabilistic results are summarised in Table 11.

Table 11: Probabilistic results: SA6 and SA7

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
SA6 2 year horizon - all receive repeat + no attendances for UC (a)									
Xeomin	£5,614	0.817	£5,614	0.045	£125,171	£4,717	£4,269	0%	0%
UC	£0	0.772							
Dysport 500U	£2,739	0.819	£2,739	0.077	£35,709	£1,205	£438	0%	22%
UC	£0	0.743							
Dysport 1000U	£3,950	0.828	£3,950	0.085	£46,308	£2,244	£1,391	0%	2%
UC	£0	0.742							
BOTOX	£4,788	0.801	£4,788	0.023	£206,515	£4,325	£4,093	0%	0%
UC	£0	0.778							
SA7 2 year horizon - all receive repeat + attendances for UC (a)									
Xeomin	£5,614	0.816	£4,879	0.045	£108,672	£3,981	£3,532	0%	0%
UC	£735	0.771							
Dysport 500U	£2,739	0.818	£2,004	0.077	£26,086	£467	n/a	12%	69%
UC	£735	0.742							
Dysport 1000U	£3,950	0.829	£3,215	0.085	£37,619	£1,506	£651	0%	16%
UC	£735	0.744							
BOTOX	£4,788	0.800	£4,053	0.023	£174,693	£3,589	£3,357	0%	0%
UC	£735	0.777							

Abbreviations: ICER = incremental cost effectiveness ratio; n/a = not applicable; QALYs = quality adjusted life years; SA = scenario analysis; UC = usual care. Threshold analysis estimates the magnitude of downstream savings needed for BoNT-A to be cost-effective at different cost effectiveness thresholds.

(a) Each type of BoNT-A is compared to the usual care arm from its respective trial (Xeomin (Elovic 2016)[6], Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA8/9: 2 year horizon, Shaw/BoTULS data on repeat extrapolated +/- neurology attendances for usual care / those not receiving repeat injections

When a two-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010)[25] for the first year and extrapolated for the second year using a trendline, up to a total of 8 injection cycles over two years, only Dysport (500U) was cost-effective compared to usual care (ICER: £15,078 per QALY, probability cost effective 82%) in the analysis where the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances (SA9). All other BoNT-A were not cost effective compared to usual care at £20,000 per QALY.

As in the other scenario analyses, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. The ICERs were lower for SA9, where the usual care arm and those not receiving repeat injections had twice yearly follow up attendances to manage their spasticity when compared to SA8. When a threshold analysis was conducted to estimate the magnitude of downstream savings over the 2-year time horizon required for BoNT-A to be cost effective at £20,000 per QALY this was lowest for Dysport (500U) in SA8: £44, and highest for Xeomin in SA8: £2,289. All probabilistic results are summarised in Table 12.

Table 12: Probabilistic results: SA8 and SA9

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
SA8 2 year horizon - Shaw 2010 data on repeats extrapolated + no attendances for UC/non-responders (a)									
Xeomin	£3,181	0.816	£3,181	0.045	£71,372	£2,289	£1,844	0%	0%
UC	£0	0.771							
Dysport 500U	£1,564	0.818	£1,564	0.076	£20,573	£44	n/a	44%	89%
UC	£0	0.742							
Dysport 1000U	£2,240	0.828	£2,240	0.085	£26,228	£532	n/a	13%	68%
UC	£0	0.743							
BOTOX	£2,716	0.800	£2,716	0.023	£118,299	£2,257	£2,028	0%	0%
UC	£0	0.777							
SA9 2 year horizon - Shaw 2010 data on repeats extrapolated + attendances for UC/non-responders (a)									
Xeomin	£3,496	0.817	£2,761	0.045	£61,583	£1,864	£1,416	0%	0%
UC	£735	0.772							
Dysport 500U	£1,884	0.819	£1,148	0.076	£15,078	n/a	n/a	82%	97%
UC	£735	0.743							

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Dysport 1000U	£2,558	0.829	£1,822	0.086	£21,140	£98	n/a	40%	87%
UC	£735	0.742							
BOTOX	£3,033	0.801	£2,298	0.023	£99,752	£1,837	£1,607	0%	0%
UC	£735	0.777							

Abbreviations: ICER = incremental cost effectiveness ratio; n/a = not applicable; QALYs = quality adjusted life years; SA = scenario analysis; UC = usual care. Threshold analysis estimates the magnitude of downstream savings needed for BoNT-A to be cost-effective at different cost effectiveness thresholds.

(a) Each type of BoNT-A is compared to the usual care arm from its respective trial (Xeomin (Elovic 2016)[6], Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA10/11: 2 year horizon, Shaw/BoTULS data, injection 5-8 same as % at injection 4, +/- neurology attendances for usual care / those not receiving repeat injections

When a 2-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010)[25] for the first year and in the second year it was assumed the proportion receiving injections 5 to 8 was the same as the proportion receiving injection 4, only Dysport (500U) was cost-effective compared to usual care (ICER: £16,191 per QALY, probability cost effective 76%) in the analysis where the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances (SA11). All other BoNT-A were not cost effective compared to usual care at £20,000 per QALY.

As the other scenario analyses, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. The ICERs were lower for SA11, where the usual care arm and those not receiving repeat injections had twice yearly follow up attendances to manage their spasticity when compared to SA10. When a threshold analysis was conducted to estimate the magnitude of downstream savings over the 2-year time horizon required for BoNT-A to be cost effective at £20,000 per QALY, this was lowest for Dysport (500U) in SA10: £163, and highest for Xeomin in SA10: £2,542. All probabilistic results are summarised in Table 13..

Table 13: Probabilistic results: SA10 and SA11

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
SA10 2 year horizon - Shaw 2010 data on repeats, injection 5-8, same as % at injection 4 + no attendances for UC/non-responders (a)									
Xeomin	£3,437	0.817	£3,437	0.045	£76,798	£2,542	£2,094	0%	0%
UC	£0	0.772							
Dysport 500U	£1,688	0.819	£1,688	0.076	£22,134	£163	n/a	33%	84%

Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
UC	£0	0.743							
Dysport 1000U	£2,429	0.828	£2,429	0.085	£28,494	£724	n/a	6%	56%
UC	£0	0.743							
BOTOX	£2,935	0.801	£2,935	0.023	£127,357	£2,474	£2,243	0%	0%
UC	£0	0.778							
SA11 2 year horizon - Shaw 2010 data on repeats, injection 5-8, same as % at injection 4 + attendances for UC/non-responders (a)									
Xeomin	£3,726	0.817	£2,991	0.045	£66,231	£2,087	£1,636	0%	0%
UC	£735	0.772							
Dysport 500U	£1,977	0.819	£1,241	0.077	£16,191	n/a	n/a	76%	97%
UC	£735	0.742							
Dysport 1000U	£2,716	0.829	£1,980	0.087	£22,885	£250	n/a	29%	81%
UC	£735	0.743							
BOTOX	£3,223	0.800	£2,488	0.023	£107,211	£2,024	£1,792	0%	0%
UC	£735	0.777							

Abbreviations: ICER = incremental cost effectiveness ratio; n/a = not applicable; QALYs = quality adjusted life years; SA = scenario analysis; UC = usual care. Threshold analysis estimates the magnitude of downstream savings needed for BoNT-A to be cost-effective at different cost effectiveness threshold.

(a) Each type of BoNT-A is compared to the usual care arm from its respective trial (Xeomin (Elovic 2016)[6], Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

4 Discussion

4.1 Summary of results

Single BoNT-A injections were not cost effective. Repeat injections not cost effective if given to all people, irrespective of response or assessment of need. Repeat BoNT-A injection may be cost effective only when all the following conditions met:

- 500U Dysport used for upper limb spasticity
- Proportion receiving repeat injections decreases over 1 or 2-year period (repeats given based on an assessment of need)
- Standard spasticity care includes twice yearly neurology attendances (therefore lowering administration costs for BoNT-A)

The results are driven by higher proportion of responders in Dysport trial and lower cost of Dysport.

4.2 Limitations and interpretation

The committee discussed that it was unclear what current practice is in terms of follow up attendances for people with spasticity but not receiving BoNT-A. If they have no regular follow up attendances then BoNT-A is unlikely to be cost effective.

This analysis is based on single RCTs (no meta-analysis possible) and not all indications reported here (upper and lower limb for each drug). Many other BoNT-A RCTS were identified in the clinical review, however only these three RCTs reported the same outcome used in the economic model (MAS). It is not clear if they are representative of the full body of clinical evidence.

The RCTs included in this analysis do not include use BoNT-A treatment in the sub-acute stroke stage and therefore, benefits on contractures are not incorporated.

This analysis has not accounted for the longer time between injections reported in an observation trial (ULIS-III).[29] Increasing the duration between injections could result in either less injections for the same QALY gain or same number of injections but a longer QALY benefit. Therefore, the current model may underestimate the cost effectiveness of BoNT-A compared to an approach which allows longer intervals between injections (lowering costs and/or raising QALYs).

Uncertainty remains as to whether benefits in downstream costs could be realised in practice, more research required to quantify this potential saving.

4.3 Generalisability to other populations or settings

Some concerns have been noted with using the EQ-5D data from the Makino 2019[13] health economic model. Firstly, the EQ-5D data is provided by responder status not by randomised group and it is unclear if any adjustments were made to account for potential confounders. EQ-5D questionnaire collection times were not reported, and therefore it is not clear if these were done when the effects of treatment are expected to peak (approximately 4 weeks) or if they were done once the effects had started to diminish over time. According to Makino 2019,[13] Australian preference weights were applied. Finally, Kanovsky 2009[11] was an RCT in upper limb spasticity and using 400U Xeomin, therefore the EQ-5D data may be less applicable to lower limb spasticity benefits or to other BoNT-A types or doses.

The committee discussed the potentially higher costs of administration of BoNT-A in people with higher dependency due to the need for at home treatment or alternatively the need for

transportation and longer outpatient appointments to account for any assistance required. It was also noted that the QoL benefit may be different in these people too. Therefore, the results of this analysis may not be generalisable to people with higher dependency.

4.4 Comparisons with published studies

There were five published health economic studies identified in the literature review. Of these, Shackley 2012[24] found that Dysport (505U) for upper limb spasticity was not cost effective compared to usual care (ICER £93,500 per QALY). This analysis had a 12-week time horizon. This compares to an ICER of £41,110 per QALY for Dysport (500U) versus usual care in the 12-week analysis presented in SA1. Shackley 2012, unlike this new analysis uses direct EQ-5D data.

Doan 2013[5] found that BOTOX (221U) was cost effective in one scenario (ICER £10,271 per QALY) where some of the health care resource use from BoTULS was utilised and not cost effective when this was excluded (£27,134 per QALY). These ICERs were over a 5-year horizon. In the new analysis, BOTOX (300U) had ICERs of more than £100,000 per QALY over 2 years. Of note, the incremental QALYs observed in Doan 2013 were much larger than those observed in the new analysis.

A direct comparison with Makino 2019 is difficult as the latter compared unlimited repeat injections of Xeomin (325U) to limited repeat injections (4 cycles), with unlimited repeats not being cost effective (ICER £28,457 per QALY). However, the de novo analysis suggests repeats without assessment of need is not cost effective (SA2, SA3, SA6 and SA7) and so does align with the conclusion of Makino 2019.

Danchenko 2022[4] found that Dysport dominates BOTOX (in both upper and lower limb). The de novo analysis suggests only Dysport (500U) may be a cost effective BoNT-A (under specific circumstances outlined in the summary above). Of note, 1-year QALYs were greater in Danchenko 2022[4] than in the de novo analysis.

Finally, Lindsay 2022[12] which looked at early use of BOTOX versus usual care and found that cost savings and mean differences of the BI and ARAT were not significant but that cost savings of £1,481 for the treatment of contractures were observed. A direct comparison to the de novo model is not feasible as the latter is not looking at early treatment or the impact on contractures. It does however confirm no downstream savings with BoNT-A (as seen in Shackley/BoTULS)[24] but suggests early BoNT-A could lead to savings from reduced contractures.

4.5 Conclusions

Cost effectiveness of BoNT-A remains uncertain. It may be cost-effective in very specific circumstances, outlined below:

- 500U Dysport used for upper limb spasticity
- Proportion receiving repeat injections decreases over 1 or 2-year period (repeats given based on an assessment of need)
- Standard spasticity care includes twice yearly neurology attendances (therefore lowering administration costs for BoNT-A)

4.6 Implications for future research

Further research may be warranted on BoNT-A treatment, where direct EQ5-D data and long-term healthcare resource use following BoNT-A treatment are collected. This should include a protocol where participants are provided with repeat injections following an assessment of need.

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