National Institute for Health and Care Excellence

Final

Stroke rehabilitation in adults (update)

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

NICE guideline NG236

Economic analysis report

October 2023

Final

This report was developed by NICE

NICE accredited
www.nice.org.uk/accreditation

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright
© NICE 2023. All rights reserved. Subject to Notice of rights.

ISBN: 978-1-4731-5474-2

Contents

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)[26] 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)[14] 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)[13] 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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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.[18] 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 and 5-year analyses. 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. At the time of guideline development, Xeomin was not licensed for use in lower limb spasticity and so was not a comparator in the lower limb model population. During the consultation phase of the guideline (June 2023), Xeomin received a new licensed indication focal spasticity of the lower limb affecting the ankle joint. As this was past the cut of phase for searches and significant changes to the cost-effectiveness analysis, this comparator was not added to the model. 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-, 2- and 5-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).[27, 31] Therefore, a 1-year time horizon was deemed sufficient to capture the impact of

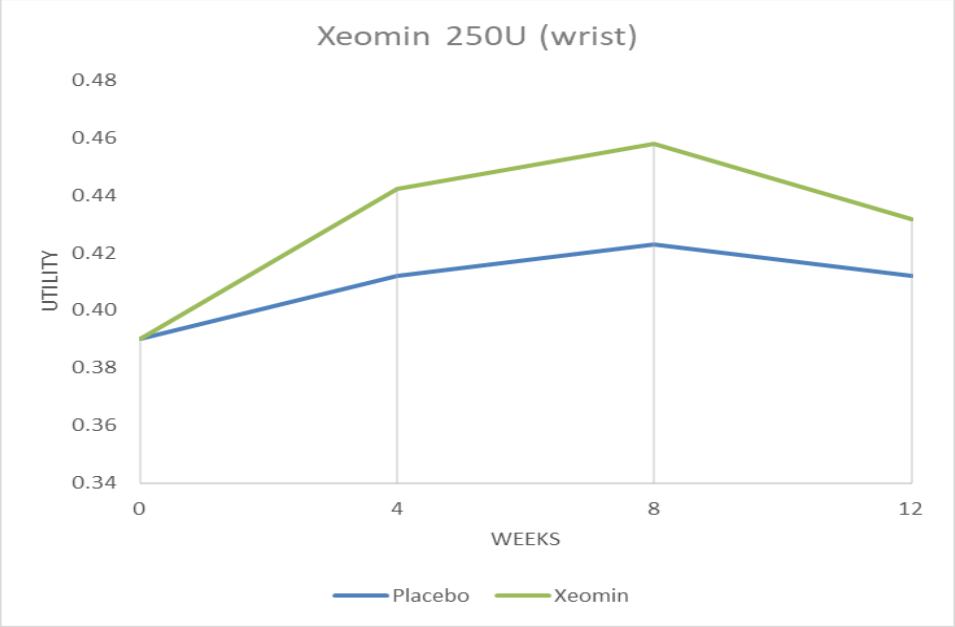
© NICE 2023. All rights reserved. Subject to Notice of rights.

repeat injections of BoNT-A. A sensitivity analysis was conducted exploring a longer 2-year and 5-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, 35] 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.[14]

The area under the curve approach is illustrated for Xeomin 250U (wrist as target clinical pattern) 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-, 2- and 5- 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 and therefore most analyses were undertaken with a 12-week interval.[31] The cost of injections was calculated by estimating the number of injections over the time horizon based on a 12 week interval, therefore for a 1-year horizon a total of 5 injections were given, at week 0, 12, 24, 36 and 48 weeks, A longer time horizon of 2 and 5 years were explored, with up to 9 and 22 injections received respectively. The total number of injections on average a year was 4.3 injections over the 5-year horizon. Sensitivity analyses explored a longer time interval of 14 weeks and 25 weeks (see 'Uncertainty' section below). The proportion receiving repeat injections progressively decreased over time. This was based on observational and UK RCT evidence (Turner Stokes 2021, Shaw 2010).[27, 31] Further detail provided in the section on 'baseline probabilities'.

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-

© NICE 2023. All rights reserved. Subject to Notice of rights.

responders will remain non-responders. The costs however will decrease if fewer people receive repeat injections over time.

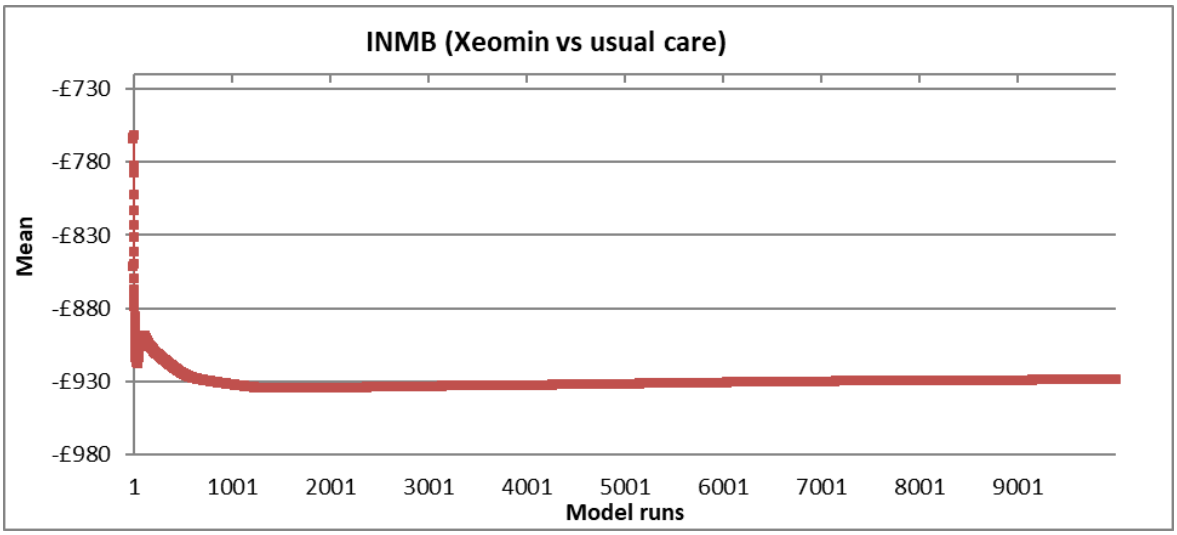
The costs of administration and the drugs are included in this analysis. The impact of BoNT-A on downstream costs were considered uncertain and therefore a threshold analysis was conducted to estimate magnitude of savings needed for BoNT-A to be cost-effective.

2.2.1 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 250U (wrist as target clinical pattern) 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



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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 having a repeat injection	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 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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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-, 2- and 5-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
Comparators	Upper limb • Xeomin 250U • Xeomin 400U • Dysport 500U • Dysport 1000U • Usual care (using placebo data) Lower limb • BOTOX 300U • Usual care (using placebo data)	Masakado 2020 (Data on file REF 1771), [15] Gracies 2015[8] and Wein 2018[35]	n/a
Population	Adults with post stroke upper limb spasticity Adults with post stroke lower limb spasticity	Masakado 2020 (Data on file REF 1771),[15] Gracies 2015[8] and Wein 2018[35]	n/a
Perspective	UK NHS & PSS	NICE reference case[18]	n/a
Time horizon	12 weeks, 1, 2 and 5 years.	12 week: Masakado 2020 (Data on file REF 1771),[15] Gracies 2015[8] and Wein 2018[35] 1,2 and 5 years: Shaw 2010,[27] extrapolation and assumptions.	n/a
Discount rate	For 2- and 5-year analyses only: Costs: 3.5% Outcomes: 3.5%	NICE reference case[18]	n/a
Baseline probabilities			
Proportion of MAS responders in placebo arm vs 250U (Wrist as target clinical pattern) – Xeomin study[a]	0 weeks: 0% 4 weeks: 27.3% 8 weeks: 27.3% 12 weeks: 27.3%	Masakado 2020 (Data on file REF 1771),[15]	Beta distribution alpha=3; beta=8 alpha=3; beta=8 alpha=3; beta=8
Proportion of MAS responders in	0 weeks: 0% 4 weeks: 36.4%	Masakado 2020 (Data on file REF 1771),[15]	Beta distribution alpha=8: beta=14

© NICE 2023. All rights reserved. Subject to Notice of rights.

Input	Data	Source	Probability distribution
placebo arm vs 400U (Wrist as target clinical pattern) – Xeomin study[a]	8 weeks: 45.5% 12 weeks: 31.8%		alpha=10; beta=12 alpha=7; beta=15
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[35]	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 250U (Wrist as target clinical pattern) versus placebo (SE)	0 weeks: 0% 4 weeks: 42% (13%) 8 weeks: 42% (13%) 12 weeks: 38% (14%)	Masakado 2020 (Data on file REF 1771),[15]	Normal distribution
Mean difference in proportion of MAS responders: Xeomin 400U (Wrist as target clinical pattern) versus placebo (SE)	0 weeks: 0% 4 weeks: 45% (10%) 8 weeks: 30% (11%) 12 weeks: 18% (11%)	Masakado 2020 (Data on file REF 1771),[15]	Normal distribution
Mean difference in proportion of MAS responders: Dysport 500U versus placebo (SE)	0 weeks: 0% 4 weeks: 51% (6%) 12 weeks: 29% (6%) 16 weeks: 15% (4%) 20 weeks: 10% (3%)	Gracies 2015[8]	Normal distribution
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[35]	Normal distribution
Repeat injections			
Time between repeat injections	12 weeks	Shaw 2010[27]	n/a

© NICE 2023. All rights reserved. Subject to Notice of rights.

Input	Data	Source	Probability distribution
(basecase)			
Proportion receiving repeat injections 1st year	2nd injection: 67.7% 3rd injection: 61% 4th injection: 51.4% 5th injection: 46.5%	Shaw 2010[27] 5th injection extrapolation of Shaw 2010,[27] using a power trendline.	Beta distribution alpha=70; beta=33 alpha=63; beta=7 alpha=53; beta=10 alpha=48; beta=5
Scenario analyses: Repeat injections			
Proportion receiving repeat injections 2nd year (extrapolation)[b]	6th injection: 42.7% 7th injection: 39.7% 8th injection: 37.3% 9th injection: 35.3%	Extrapolation of Shaw 2010, [27] using a power trendline.	Beta distribution alpha=44; beta=4 alpha=41; beta=3 alpha=38; beta=2 alpha=36; beta=2
Proportion receiving repeat injections 1st and 2nd year (assumption 5th to 9th = 4th injection)	2nd injection: 67.7% 3rd injection: 61% 4th to 9th injection: 51.4%	Assumption based on Shaw 2010[27]	Beta distribution alpha=70; beta=33 alpha=63; beta=7 alpha=53; beta=10
All receiving repeat injections 1st and 2nd year	Each injection (2nd to 9th): 100%	Assumption	fixed
Health-related quality of life (utilities)			
Responder utility (SE)	0.51 (0.02)	Makino 2019[14]	Beta distribution alpha=305; beta=294
Non-responder utility (SE)	0.39 (0.02)	Makino 2019[14]	Beta distribution alpha=222; beta=348
Costs			
Xeomin 250U / 400U	[redacted] £324.75 / £519.60	Confidential Patient Access Scheme cost. 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 of BoNT-A	£244	Neurology, Consultant-led Multiprofessional Non-Admitted Face-to-Face Attendance, First. NHS reference costs 2019/2020[22]	n/a
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[22]	n/a

(a) Finger and Elbow as target clinical pattern also explored, fully reported in 2.3.2 Baseline probabilities.
(b) 5-year extrapolation of Shaw 2010 fully reported in 2.3.2 Baseline probabilities.
Abbreviations: BoNT-A = botulinum toxin A; MAS = Modified Ashworth Scale; n/a = not applicable; SE = standard error, U = units.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 250U, wrist as target clinical pattern (Masakado 2020, Data on file REF 1771),[15]	0 weeks: 0% 4 weeks: 27.3% 8 weeks: 27.3% 12 weeks: 27.3%	N=11	Beta distribution alpha=3; beta=8 alpha=3; beta=8 alpha=3; beta=8
Xeomin 400U, wrist as target clinical pattern (Masakado 2020, Data on file REF 1771),[15]	0 weeks: 0% 4 weeks: 36.4% 8 weeks: 45.5% 12 weeks: 31.8%	N=22	Beta distribution alpha=8: beta=14 alpha=10; beta=12 alpha=7; beta=15
Xeomin 250U, finger as target clinical pattern (Masakado 2020, Data on file REF 1771),[15]	0 weeks: 0% 4 weeks: 18.2% 8 weeks: 27.3% 12 weeks: 36.4%	N=11	Beta distribution alpha=2; beta=9 alpha=3; beta=8 alpha=4; beta=7
Xeomin 400U, finger as target clinical pattern (Masakado 2020, Data on file REF 1771),[15]	0 weeks: 0% 4 weeks: 27.3% 8 weeks: 31.8% 12 weeks: 13.6%	N=22	Beta distribution alpha=6: beta=16 alpha=7; beta=15 alpha=3; beta=19
Xeomin 250U, elbow as target clinical pattern (Masakado 2020, Data on file REF 1771),[15]	0 weeks: 0% 4 weeks: 18.2% 8 weeks: 27.3% 12 weeks: 18.2%	N=11	Beta distribution alpha=2; beta=9 alpha=3; beta=8 alpha=2; beta=9
Xeomin 400U, elbow as target clinical pattern (Masakado 2020, Data on file REF 1771),[15]	0 weeks: 0% 4 weeks: 18.2% 8 weeks: 31.8% 12 weeks: 9.1%	N=22	Beta distribution alpha=4: beta=18 alpha=7; beta=15 alpha=2; beta=20
Dysport (Gracies 2015)[8]	0 weeks: 0% 4 weeks: 23%	N=79	Beta distribution alpha=18; beta=61

© NICE 2023. All rights reserved. Subject to Notice of rights.

Drug (Study)	% MAS responders placebo	Sample size	Probability distribution
	12 weeks: 14% 16 weeks: 4% 20 weeks: 0%		alpha=11; beta=68 alpha=3; beta=76
BOTOX (Wein 2018)[35]	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.[35] 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),[27] 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. Repeats were given based on an assessment of need.

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)[30] 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. An open label extension of a Xeomin RCT reported a 99-day median interval between treatment cycles (14.1 weeks).[11] ULIS-III (Turner-Stokes 2021)[31] 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, with the mean injection interval of 177.6 (SD 81.9) [57–644] days (25.3 weeks). 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. Given the evidence on longer intervals has not been appraised as part of the clinical review (studies were observational or open label extensions) a 12-week interval was assumed for most analyses. A longer interval was explored in two sensitivity analyses in the model, one using a 14-week interval and another a 25-week interval, in these analyses it is assumed that the QALY gain was maintained but the costs (fewer injections) were reduced.

Based on this information, one scenario was explored where, over a 1-year time horizon, people would receive up to 5 cycles of BoNT-A injections (one injection cycle every 12 weeks) and that the proportions having the repeat cycles would decrease and be taken from BoTULS trial (Shaw 2010, and extrapolation for the 5th injection cycle, see below).[27] Some committee members thought that this may be underestimating the proportion of people

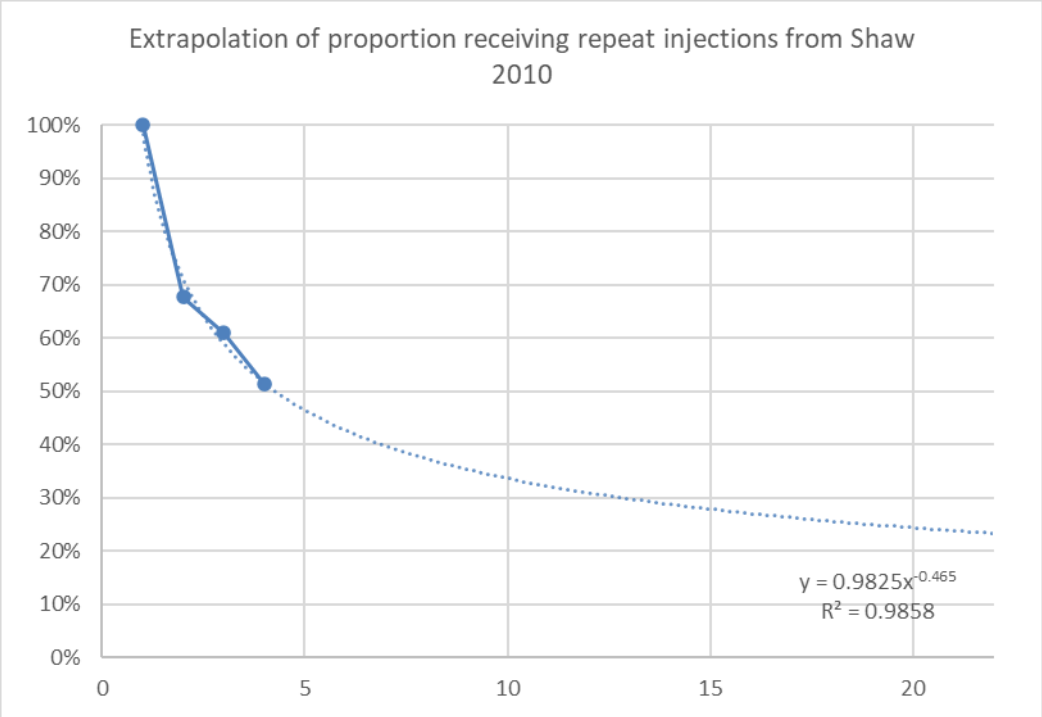
© NICE 2023. All rights reserved. Subject to Notice of rights.

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 and 5-year time horizon were explored where the 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 beyond injection cycle 4 (see Figure 2). The LINEST function was used to generate the power trendline equation values.

A 2-year time horizon was explored where the proportion receiving injections injections 5 onwards was 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[27]

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 with extrapolation for 5th injection)[27]	2nd injection: 67.7% 3rd injection: 61% 4th injection: 51.4% 5th injection: 46.5%	N=103	Beta distribution (a) alpha=70; beta=33 alpha=63; beta=7 alpha=53; beta=10 alpha=48; beta=5
Proportion receiving repeat injections beyond injection cycle 4	6th injection: 42.7% 7th injection: 39.7% 8th injection: 37.3% 9th injection: 35.3%	Assume n=103	Beta distribution (a) alpha=44; beta=4 alpha=41; beta=3 alpha=38; beta=2

© NICE 2023. All rights reserved. Subject to Notice of rights.

Scenario and source	% receiving repeat injections	Sample size	Probability distribution
(Shaw 2010[27] with extrapolation)	10th injection: 33.6% 11th injection: 32.2% 12th injection: 30.9% 13th injection: 29.8% 14th injection: 28.8% 15th injection: 27.9% 16th injection: 27.0% 17th injection: 26.3% 18th injection: 25.6% 19th injection: 25.0% 20th injection: 24.4% 21st injection: 23.8% 22nd injection: 23.3%		alpha=36; beta=2 alpha=35; beta=2 alpha=33; beta=2 alpha=32; beta=1 alpha=31; beta=1 alpha=30; beta=1 alpha=29; beta=1 alpha=28; beta=1 alpha=27; beta=1 alpha=26; beta=1 alpha=26; beta=1 alpha=25; beta=1 alpha=25; beta=1 alpha=24; beta=1
Proportion receiving repeat injections 1st and 2nd year (assumption 5th to 9th = 4th injection)	2nd injection: 67.7% 3rd injection: 61% 4th to 9th injection: 51.4%	Assumption based on Shaw 2010[27]	Beta distribution alpha=70; beta=33 alpha=63; beta=7 alpha=53; beta=10
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.

Although the proportions do not correlate directly with the proportion of MAS responders for each BoNT-A from the individual RCTs (as outlined in the section below), this was considered the best available evidence on the proportion receiving repeats over time given there was no longitudinal data on the proportion of responders who receive repeat injections from RCT data identified in the clinical review. A sensitivity analysis has been conducted, to explore extrapolating the 12 weeks RCT MAS responder data, using the rate of discontinuation from Shaw 2010 and its extrapolation, further details are outline in section 2.5 Sensitivity analyses.

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[27] and Wallace 2020[33]). Shaw 2010[27] is an RCT of Dysport (500U) for upper limb spasticity used in one of the published CUA summarised in the evidence review (Shackley 2012)[26] and the second RCT, Wallace 2020[33], 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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)[24, 28, 29] 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[32]. 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.[17] 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[14] utilised EQ-5D values by MAS responder status from a post-hoc analysis of Kanovsky 2009[12] (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]

Nineteen RCTs reporting MAS mean data comparing BoNT-A to usual care or placebo 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[17] 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).[35] The NG144[17] 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.[23] 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[17] 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 (Masakado 2020, Data on file REF 1771),[15] n=100, dose 250U/400U)

Lower limb spasticity:

- BOTOX versus placebo (Wein 2018,[35] n=468, dose 300U)

© NICE 2023. All rights reserved. Subject to Notice of rights.

Of note Masakado 2020,[15] reported results for three target clinical patterns, flexed wrist (wrist), clenched fist (finger) and flexed elbow (elbow). All three are included in the analysis.

The advantage of using MAS responder data for modelling is that the trials were predominantly large and all 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 RevMan to calculate the mean difference (risk 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 250U (wrist) (Masakado 2020, data on file REF 1771)[15]	0 weeks: 0% 4 weeks: 69.6% 8 weeks: 69.6% 12 weeks: 62.5%	N=23	0 weeks: 0% 4 weeks: 42% (10%, 75%) 8 weeks: 42% (10%, 75%) 12 weeks: 38% (5%, 71%)	Normal distribution SE=13% SE=13% SE=14%
Xeomin 400U (wrist) (Masakado 2020, data on file REF 1771)[15]	0 weeks: 0% 4 weeks: 81.8% 8 weeks: 75% 12 weeks: 50%	N=44	0 weeks: 0% 4 weeks: 45% (22%, 69%) 8 weeks: 30% (5%, 54%) 12 weeks: 18% (-6%, 43%)	Normal distribution SE=10% SE=11% SE=11%
Xeomin 250U (finger) (Masakado 2020, data on file REF 1771)[15]	0 weeks: 0% 4 weeks: 52.2% 8 weeks: 43.5% 12 weeks: 34.8%	N=23	0 weeks: 0% 4 weeks: 34% (29%, 75%) 8 weeks: 16% (-5%, 56%) 12 weeks: -2% (-25%, 40%)	Normal distribution SE=10% SE=13% SE=14%
Xeomin 400U (finger) (Masakado 2020, data on file REF 1771)[15]	0 weeks: 0% 4 weeks: 68.2% 8 weeks: 59.1% 12 weeks: 34.1%	N=44	0 weeks: 0% 4 weeks: 41% (53%, 83%) 8 weeks: 27% (8%, 55%) 12 weeks: 21% (-22%, 26%)	Normal distribution SE=6% SE=10% SE=10%
Xeomin 250U (elbow) (Masakado 2020, data on file REF 1771)[15]	0 weeks: 0% 4 weeks: 43.5% 8 weeks: 56.5% 12 weeks: 34.8%	N=23	0 weeks: 0% 4 weeks: 25% (21%, 66%) 8 weeks: 29% (8%, 69%) 12 weeks: 17% (-25%, 40%)	Normal distribution SE=9% SE=13% SE=14%
Xeomin 400U (elbow)	0 weeks: 0% 4 weeks: 56.8%	N=44	0 weeks: 0% 4 weeks: 39% (41%, 72%)	Normal distribution SE=7%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Drug (Study)	% MAS responders BoNT-A	Sample size	Mean difference BoNT-A vs placebo (95%CI)	Probability distribution
(Masakado 2020, data on file REF 1771)[15]	8 weeks: 52.3% 12 weeks: 34.1%		8 weeks: 21% (12%, 56%) 12 weeks: 25% (-22%, 26%)	SE=9% SE=10%
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)[35]	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.

2.3.4 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[14] 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,[12] an RCT included in clinical review. The EQ-5D data was not reported in the RCT publication and was only available in Makino 2019.[14]

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[12] 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

© NICE 2023. All rights reserved. Subject to Notice of rights.

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], with the exception of Xeomin, where confidential patient access scheme prices were used. Patient access scheme prices are confidential pricing agreements that enable flat nationally available discounts, Xeomin was the only drug where such a discount was available. This cost is not presented in this report but was used to generate model results for committee discussion during development of recommendations. Results using the PAS prices were generated and presented to the committee for all analyses. All analyses presented in this report are based on the list prices, with the results of the PAS price analyses described qualitatively.

Drug 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[(a)]	Unit cost
Xeomin 250U/400U[(c)]	50U:[(b)] £[redacted] 100U:[(b)] £[redacted] 200U:[(b)] £[redacted] 50U: £72.00 100U: £129.90 200U: £259.80	250U: £[redacted] 400U: £[redacted] 250U: £324.75 400U: £519.60
Dysport 500U/1000U[(d)]	300U: £92.40 500U: £154.00	500U: £154.00 1000U: £308.00
BOTOX 300U[(e)]	50U: £77.50 100U: £138.20 200U: £276.40	300U: £414.60

Source: (a) BNF online[2], (b) Confidential Patient Access Scheme provided by Merz Pharma UK Ltd, (c) Masakado 2020,[15] (d) Gracies 2015,[8] (e) Wein 2018[35]

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:[26, 27] 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)

© NICE 2023. All rights reserved. Subject to Notice of rights.

- Makino 2019:[14] 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:[13] one hour of therapist (band 6) time, £45 per session (PSSRU 2019)

In NICE TA260,[16] 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[25] 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[21] 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[21]	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[21]	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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

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]

2.3.6.3 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)[27] and Lindsay 2022.[13] In BoTULS when the 3-month resource use was included in the Shackley 2012[26] 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,[13] 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, 34]

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

In the 2- and 5-year time horizon analyses, 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)

2.5 Sensitivity analyses

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

SA1/2: Model within trial period and Shaw/BoTULS data on repeat, 12-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (12-weeks, 1-, 2- and 5-year horizon)

In this analysis multiple time horizons were explored including:

- 12-week time horizon where only the trial period data was utilised and therefore only a single BoNT-A injection cycle was administered.

- 1-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 5 injection cycles in one year (the 5th injection was extrapolated using a trendline).

- 2-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 9 injection cycles over 2 years (5th to 9th injections were extrapolated using a trendline).

- 5-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 22 injection cycles over 5 years (5th to 22nd injections were extrapolated using a trendline).

A 12-week interval between injection cycles was applied. This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA1) and with them receiving these attendances (SA2).

SA3/4: All receive repeat, 12-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (1- and 2-year horizon)

In this analysis all those in the BoNT-A comparator received repeat injections, irrespective of an assessment of need or assessment of response. This was explored over multiple time horizons (1- and 2-years) and a 12-week interval between injection cycles was applied. This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA3) and with them receiving these attendances (SA4).

© NICE 2023. All rights reserved. Subject to Notice of rights.

SA5/6: Shaw/BoTULS data, injection 5-9 same as % at injection 4, 12-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (2-year horizon)

In this analysis the proportion receiving repeat injections was taken from BoTULS (Shaw 2010)[27] for the first 4 injection cycles and subsequent injections cycles it was assumed the proportion receiving injections was the same as the proportion receiving injection 4. A 12-week interval between injection cycles was applied This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA5) and with them receiving these attendances (SA6).

SA7/8: Shaw/BoTULS data on repeat, 25-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

This is the same as SA1/2 but with a 25-week interval between injection cycles applied based on ULIS III observational study (Turner-Stokes 2021)[31]. Multiple time horizons were explored:

- 1-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 3 injection cycles in one year.

- 2-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 5 injection cycles over 2 years (5^{th} injection was extrapolated using a trendline).

- 5-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 11 injection cycles over 5 years (5^{th} to 11^{th} injections were extrapolated using a trendline).

This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA7) and with them receiving these attendances (SA8).

SA9/10: Shaw/BoTULS data on repeat, 14-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

This is the same as SA1/2 but with a 14-week interval between injection cycles applied based on Turner-Stokes 2013[30] and Kanovsky 2011[11]. Multiple time horizons were explored:

- 1-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 4 injection cycles in one year.

- 2-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 8 injection cycles over 2 years (5^{th} to 8^{th} injection was extrapolated using a trendline).

- 5-year horizon where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] with up to a total of 19 injection cycles over 5 years (5^{th} to 19^{th} injections were extrapolated using a trendline).

This was done without the usual care arm or those not receiving repeat injections having twice annual follow up neurology consultant-led multidisciplinary attendances (SA9) and with them receiving these attendances (SA10).

© NICE 2023. All rights reserved. Subject to Notice of rights.

SA11: Shaw/BoTULS repeats rate of repeats applied to MAS responder RCT data, 12-week interval between repeats, with neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

In this analysis the proportion receiving repeat injections was estimated by applying the rate from BoTULS (Shaw 2010)[27] , including the extrapolation with trendline, to the highest proportion of MAS responders from each RCT informing the model. The resulting proportions are detailed in Table 8 below. Of note, only Xeomin wrist was included in this analysis and all proportion of repeats were fixed in the probabilistic analysis.

Table 8: Proportion repeats based on MAS responder RCT data

Injection cycle	Shaw extrapolation (a)	Xeomin 250U wrist	Xeomin 400U wrist	Dysport 500U	Dysport 1000U	BOTOX
1	100.0%	100%	100%	100%	100%	100%
2	67.7%	**69.60%**(b)	**81.80%**(b)	**74%**(c)	**79%**(c)	**53%**(d)
3	61.0%	63%	74%	67%	71%	48%
4	51.4%	53%	62%	56%	60%	40%
5	46.5%	48%	56%	51%	54%	36%
6	42.7%	44%	52%	47%	50%	33%
7	39.7%	41%	48%	43%	46%	31%
8	37.3%	38%	45%	41%	44%	29%
9	35.3%	36%	43%	39%	41%	28%
10	33.6%	35%	41%	37%	39%	26%
11	32.2%	33%	39%	35%	38%	25%
12	30.9%	32%	37%	34%	36%	24%
13	29.8%	31%	36%	33%	35%	23%
14	28.8%	30%	35%	31%	34%	23%
15	27.9%	29%	34%	30%	33%	22%
16	27.0%	28%	33%	30%	32%	21%
17	26.3%	27%	32%	29%	31%	21%
18	25.6%	26%	31%	28%	30%	20%
19	25.0%	26%	30%	27%	29%	20%
20	24.4%	25%	29%	27%	28%	19%
21	23.8%	24%	29%	26%	28%	19%
22	23.3%	24%	28%	25%	27%	18%

Sources: (a) Shaw 2010[27] (b) Masakado 2020,[15] (c) Gracies 2015,[8] (d) Wein 2018[35]

A 12-week interval between injection cycles was applied. This was done only with the usual care arm or those not receiving repeat injections having twice annual follow up neurology

© NICE 2023. All rights reserved. Subject to Notice of rights.

consultant-led multidisciplinary attendances, as this was a more favourable scenario for BoNT-A treatments.

SA12: Shaw/BoTULS repeats rate of repeats applied to MAS responder RCT data, 25-week interval between repeats, with neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

This analysis was the same as SA11, however a 25-week interval between injection cycles was applied, and therefore up to a total of 3, 5 and 11 injection cycles were given over 1-,2- and 5-year horizons.

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.[18-20] 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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

3 Results

The results of the analyses based on list prices for all drugs, including Xeomin are presented below. It should be noted that these results were not used by the committee when drafting recommendations for this review question, as they do not take into account the confidential discount associated with Xeomin. The committee was presented with the results with the confidential PAS discount for Xeomin applied and used these results as the basis for their recommendations. These results cannot be presented here due to their commercially sensitive nature, however a narrative summary is provided. For all analyses the probabilistic and deterministic results were very similar and the conclusions regarding overall cost effectiveness were the same, therefore only the probabilistic results were presented as they quantify uncertainty in the results. Only results for Xeomin wrist as target clinical pattern are presented in the tables in this section, the other targets are reported in Appendix A, however cost effective results are highlighted narratively for all targets.

The threshold analyses indicated the magnitude of downstream savings over each time horizon required for BoNT-A to be cost effective at £20,000 per QALY, these are summarised in the results tables. Overall this was lowest for Dysport (500U) (or Xeomin 250U wrist if Dysport 500U was cost effective) and highest for BOTOX. In most scenarios substantial downstream savings are required for BOTOX to be cost effective.

SA1/2: Model within trial period and Shaw/BoTULS data on repeat, 12-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (12-weeks, 1-, 2- and 5-year horizon)

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 £205 for Dysport (500U) to £600 for BOTOX. 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 0-3% versus usual care.

When a 1-year time horizon was explored, where the proportion receiving repeat injections was taken/extrapolated from BoTULS (Shaw 2010),[27] up to a total of 5 injection cycles in one year, none of the BoNT-A drugs were cost effective compared to usual care at a threshold of £20,000 per QALY. The lowest observed ICER was for Dysport (500U) compared to usual care (£22,938 per QALY probability cost effective 27%) 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 (SA2). As seen at 12-weeks, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care. The ICERs were lower for SA2, where the usual care arm and those not receiving repeat injections had twice yearly follow up attendances to manage their spasticity when compared to SA1.

When a 2-year time horizon was explored, where the proportion receiving repeat injections was taken/extrapolated from BoTULS (Shaw 2010),[27] up to a total of 9 injection cycles over 2 years, only Dysport (500U) compared to usual care was cost effective (ICER: £16,191 per QALY,

© NICE 2023. All rights reserved. Subject to Notice of rights.

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 (SA2). As seen at 12-weeks and 1-year, the ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care and lower for SA2 compared to SA1.

When a 5-year time horizon was explored, where the proportion receiving repeat injections was taken/extrapolated from BoTULS (Shaw 2010),[27] up to a total of 22 injection cycles over 5 years, Dysport (500U and 1000U) are cost-effective compared to usual care both with and without the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances. The ICER was lowest for Dysport 500U (SA1: £14,219 per QALY, SA2: £11,392 per QALY) and then Dysport 1000U (SA1: £18,286 per QALY, SA2: £15,570 per QALY). Using the list price, Xeomin 250U wrist was cost effective when neurology attendances were excluded but when PAS prices were applied for Xeomin 250U wrist was cost effective both with and without neurology attendances. BOTOX had the highest ICER.

Probabilistic results for SA1 and SA2 are summarised in Table 9 and Table 10.

Table 9: Probabilistic results SA1 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
12 week	Xeomin 250U	£568.75	0.1057	£568.75	0.0095	£59,889.90	£378.82	£283.85	0%	0%
	UC	£0.00	0.0962							
1 year	Xeomin 250U	£1,726.30	0.4580	£1,726.30	0.0412	£41,949.34	£903.26	£491.74	0%	12%
	UC	£0.00	0.4168							
2 years	Xeomin 250U	£2,490.95	0.9004	£2,490.95	0.0809	£30,785.88	£872.71	£63.59	7%	44%
	UC	£0.00	0.8195							
5 years	Xeomin 250U	£4,153.75	2.1401	£4,153.75	0.1923	£21,599.69	£307.63	n/a	38%	80%
	UC	£0.00	1.9478							
12 week	Xeomin 400U	£763.60	0.1069	£763.60	0.0078	£97,944.76	£607.68	£529.71	0%	0%
	UC	£0.00	0.0991							
1 year	Xeomin 400U	£2,363.82	0.4632	£2,363.82	0.0338	£69,969.42	£1,688.15	£1,350.31	0%	0%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£0.00	0.4295							
2 years	Xeomin 400U	£3,421.41	0.9108	£3,421.41	0.0664	£51,507.98	£2,092.91	£1,428.67	0%	2%
	UC	£0.00	0.8444							
5 years	Xeomin 400U	£5,714.84	2.1648	£5,714.84	0.1579	£36,198.80	£2,557.36	£978.63	2%	25%
	UC	£0.00	2.0069							
Dysport										
12 week	Dysport 500U	£398.00	0.1040	£398.00	0.0097	£41,120.47	£204.42	£107.63	0%	9%
	UC	£0.00	0.0943							
1 year	Dysport 500U	£1,169.32	0.4507	£1,169.32	0.0419	£27,879.58	£330.48	n/a	8%	59%
	UC	£0.00	0.4087							
2 years	Dysport 500U	£1,678.84	0.8861	£1,678.84	0.0825	£20,358.17	£29.54	n/a	46%	88%
	UC	£0.00	0.8036							
5 years	Dysport 500U	£2,786.83	2.1059	£2,786.83	0.1960	**£14,218.73**	n/a	n/a	85%	98%
	UC	£0.00	1.9099							
12 week	Dysport 1000U	£552.00	0.1054	£552.00	0.0109	£50,839.92	£334.85	£226.27	0%	0%
	UC	£0.00	0.0945							
1 year	Dysport 1000U	£1,673.02	0.4567	£1,673.02	0.0470	£35,558.55	£732.02	£261.53	0%	24%
	UC	£0.00	0.4096							
2 years	Dysport 1000U	£2,413.90	0.8979	£2,413.90	0.0925	£26,093.87	£563.73	n/a	13%	69%
	UC	£0.00	0.8054							
5 years	Dysport 1000U	£4,020.53	2.1341	£4,020.53	0.2199	**£18,286.22**	n/a	n/a	61%	94%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£0.00	1.9142							
BOTOX										
12 week	BOTOX	£658.60	0.1017	£658.60	0.0029	£225,414.47	£600.17	£570.95	0%	0%
	UC	£0.00	0.0988							
1 year	BOTOX	£2,019.38	0.4407	£2,019.38	0.0127	£159,498.28	£1,766.16	£1,639.56	0%	0%
	UC	£0.00	0.4281							
2 years	BOTOX	£2,918.29	0.8666	£2,918.29	0.0249	£117,231.05	£2,420.42	£2,171.49	0%	0%
	UC	£0.00	0.8417							
5 years	BOTOX	£4,873.04	2.0596	£4,873.04	0.0592	£82,363.42	£3,689.73	£3,098.08	0%	0%
	UC	£0.00	2.0005							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

Table 10: Probabilistic results SA2 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
12 week	Xeomin 250U	£568.75	0.1057	£568.75	0.0095	£60,021.06	£379.23	£284.47	0%	0%
	UC	£0.00	0.0962							
1 year	Xeomin 250U	£1,892.89	0.4581	£1,518.89	0.0411	£36,990.08	£697.65	£287.03	1%	22%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£374.00	0.4170							
2 years	Xeomin 250U	£2,883.60	0.9007	£2,148.24	0.0807	£26,608.46	£533.54	n/a	16%	62%
	UC	£735.35	0.8200							
5 years	Xeomin 250U	£5,349.88	2.1407	£3,602.15	0.1919	**£18,772.37**	n/a	n/a	55%	90%
	UC	£1,747.73	1.9491							
12 week	Xeomin 400U	£763.60	0.1067	£763.60	0.0078	£98,244.99	£608.15	£530.43	0%	0%
	UC	£0.00	0.0989							
1 year	Xeomin 400U	£2,524.07	0.4622	£2,150.07	0.0337	£63,837.44	£1,476.46	£1,139.66	0%	0%
	UC	£374.00	0.4286							
2 years	Xeomin 400U	£3,800.57	0.9088	£3,065.22	0.0662	£46,287.03	£1,740.78	£1,078.56	0%	6%
	UC	£735.35	0.8426							
5 years	Xeomin 400U	£6,883.76	2.1600	£5,136.03	0.1574	£32,632.25	£1,988.21	£414.29	4%	37%
	UC	£1,747.73	2.0027							
Dysport										
12 week	Dysport 500U	£398.00	0.1042	£398.00	0.0097	£41,198.72	£204.79	£108.19	0%	8%
	UC	£0.00	0.0945							
1 year	Dysport 500U	£1,334.24	0.4514	£960.24	0.0419	£22,938.25	£123.00	n/a	27%	82%
	UC	£374.00	0.4095							
2 years	Dysport 500U	£2,068.02	0.8874	£1,332.67	0.0823	**£16,191.10**	n/a	n/a	76%	97%
	UC	£735.35	0.8051							
5 years	Dysport 500U	£3,976.38	2.1092	£2,228.65	0.1956	**£11,392.47**	n/a	n/a	96%	100%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£1,747.73	1.9136							
12 week	Dysport 1000U	£552.00	0.1052	£552.00	0.0109	£50,512.68	£333.44	£224.16	0%	1%
	UC	£0.00	0.0943							
1 year	Dysport 1000U	£1,833.96	0.4560	£1,459.96	0.0474	£30,830.42	£512.87	£39.32	3%	44%
	UC	£374.00	0.4087							
2 years	Dysport 1000U	£2,794.61	0.8966	£2,059.26	0.0931	£22,116.96	£197.11	n/a	34%	85%
	UC	£735.35	0.8035							
5 years	Dysport 1000U	£5,193.23	2.1310	£3,445.49	0.2213	**£15,569.96**	n/a	n/a	80%	97%
	UC	£1,747.73	1.9142							
BOTOX										
12 week	BOTOX	£658.60	0.1018	£658.60	0.0029	£226,641.02	£600.48	£571.42	0%	0%
	UC	£0.00	0.0989							
1 year	BOTOX	£2,186.85	0.4410	£1,812.85	0.0126	£143,964.70	£1,561.00	£1,435.08	0%	0%
	UC	£374.00	0.4284							
2 years	BOTOX	£3,312.76	0.8671	£2,577.41	0.0248	£104,100.68	£2,082.23	£1,834.64	0%	0%
	UC	£735.35	0.8424							
5 years	BOTOX	£6,072.63	2.0610	£4,324.90	0.0588	£73,496.62	£3,148.00	£2,559.55	0%	0%
	UC	£1,747.73	2.0021							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

© NICE 2023. All rights reserved. Subject to Notice of rights.

SA3/4: All receive repeat, 12-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (1- and 2-year horizon)

When all continued to receive repeat BoNT-A injections over a 1-and 2-year time horizon, irrespective of response or assessment of need, none of the BoNT-A were cost effective at £20,000 per QALY with and without the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances (SA3/SA4). The results for SA3 and SA4 are reported in Table 11 and Table 12, respectively.

Table 11: Probabilistic results SA3 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£2,615.75	0.4585	£2,615.75	0.0411	£63,686.72	£1,794.31	£1,383.59	0%	0%
	UC	£0.00	0.4174							
2 years	Xeomin 250U	£4,593.53	0.9014	£4,593.53	0.0808	£56,882.01	£2,978.42	£2,170.87	0%	1%
	UC	£0.00	0.8207							
1 year	Xeomin 400U	£3,590.00	0.4627	£3,590.00	0.0336	£106,692.38	£2,917.04	£2,580.56	0%	0%
	UC	£0.00	0.4290							
2 years	Xeomin 400U	£6,320.82	0.9097	£6,320.82	0.0662	£95,540.69	£4,997.65	£4,336.07	0%	0%
	UC	£0.00	0.8435							
Dysport										
1 year	Dysport 500U	£1,762.00	0.4510	£1,762.00	0.0417	£42,293.37	£928.77	£512.16	0%	6%
	UC	£0.00	0.4094							
2 years	Dysport 500U	£3,079.87	0.8868	£3,079.87	0.0819	£37,598.92	£1,441.60	£622.46	0%	16%
	UC	£0.00	0.8049							
1 year	Dysport 1000U	£2,532.00	0.4564	£2,532.00	0.0472	£53,649.97	£1,588.10	£1,116.16	0%	0%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£0.00	0.4092							
2 years	Dysport 1000U	£4,445.04	0.8973	£4,445.04	0.0928	£47,902.45	£2,589.17	£1,661.23	0%	1%
	UC	£0.00	0.8045							
BOTOX										
1 year	BOTOX	£3,065.00	0.4411	£3,065.00	0.0126	£243,050.28	£2,812.79	£2,686.68	0%	0%
	UC	£0.00	0.4285							
2 years	BOTOX	£5,390.02	0.8672	£5,390.02	0.0248	£217,386.36	£4,894.13	£4,646.18	0%	0%
	UC	£0.00	0.8424							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

Table 12: Probabilistic results SA4 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£2,615.75	0.4589	£2,241.75	0.0417	£53,717.03	£1,407.10	£989.77	0%	1%
	UC	£374.00	0.4171							
2 years	Xeomin 250U	£4,593.53	0.9022	£3,858.18	0.0821	£47,020.01	£2,217.10	£1,396.56	0%	4%
	UC	£735.35	0.8201							
1 year	Xeomin 400U	£3,590.00	0.4626	£3,216.00	0.0333	£96,436.84	£2,549.03	£2,215.55	0%	0%
	UC	£374.00	0.4292							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
2 years	Xeomin 400U	£6,320.82	0.9095	£5,585.47	0.0656	£85,184.87	£4,274.09	£3,618.40	0%	0%
	UC	£735.35	0.8440							
Dysport										
1 year	Dysport 500U	£1,762.00	0.4512	£1,388.00	0.0422	£32,927.78	£544.94	£123.41	1%	35%
	UC	£374.00	0.4090							
2 years	Dysport 500U	£3,079.87	0.8871	£2,344.52	0.0829	£28,288.06	£686.92	n/a	6%	58%
	UC	£735.35	0.8042							
1 year	Dysport 1000U	£2,532.00	0.4560	£2,158.00	0.0467	£46,183.21	£1,223.46	£756.19	0%	2%
	UC	£374.00	0.4093							
2 years	Dysport 1000U	£4,445.04	0.8966	£3,709.69	0.0919	£40,378.14	£1,872.22	£953.48	0%	9%
	UC	£735.35	0.8047							
BOTOX										
1 year	BOTOX	£3,065.00	0.4411	£2,691.00	0.0127	£211,389.75	£2,436.40	£2,309.10	0%	0%
	UC	£374.00	0.4284							
2 years	BOTOX	£5,390.02	0.8674	£4,654.67	0.0250	£185,966.71	£4,154.08	£3,903.78	0%	0%
	UC	£735.35	0.8424							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

© NICE 2023. All rights reserved. Subject to Notice of rights.

SA5/6: Shaw/BoTULS data, injection 5-9 same as % at injection 4, 12-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (2-year horizon)

In this analysis, where the Shaw data was used for the proportion of repeats (injections cycles 1-4) and it was assumed that the proportion receiving injection 5-9 was equal to that receiving in injection 4, only Dysport (500U) compared to usual care was cost effective (ICER: £17,738 per QALY, probability cost effective 66%) 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 (SA6). The ICER was lowest for Dysport 500U compared to usual care and highest for BOTOX versus usual care and lower for SA5 compared to SA6.

Table 13: Probabilistic results SA5 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
2 years	Xeomin 250U	£2,767.05	0.9021	£2,767.05	0.0810	£34,154.70	£1,146.74	£336.59	3%	32%
	UC	£0.00	0.8211							
2 years	Xeomin 400U	£3,799.09	0.9101	£3,799.09	0.0661	£57,507.75	£2,477.84	£1,817.22	0%	1%
	UC	£0.00	0.8441							
Dysport										
2 years	Dysport 500U	£1,862.82	0.8876	£1,862.82	0.0824	£22,593.89	£213.86	n/a	31%	83%
	UC	£0.00	0.8051							
2 years	Dysport 1000U	£2,678.47	0.8977	£2,678.47	0.0923	£29,017.01	£832.33	n/a	5%	53%
	UC	£0.00	0.8054							
BOTOX										
2 years	BOTOX	£3,242.86	0.8677	£3,242.86	0.0248	£130,801.21	£2,747.02	£2,499.09	0%	0%
	UC	£0.00	0.8429							

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

(a) Each type of BoNT-A is compared to the usual care arm from its respective trial (Xeomin 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

Table 14: Probabilistic results SA6 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
2 years	Xeomin 250U	£3,102.61	0.9018	£2,367.26	0.0814	£29,094.29	£739.96	n/a	8%	52%
	UC	£735.35	0.8204							
2 years	Xeomin 400U	£4,138.46	0.9105	£3,403.10	0.0661	£51,519.56	£2,082.01	£1,421.47	0%	2%
	UC	£735.35	0.8444							
Dysport										
2 years	Dysport 500U	£2,197.62	0.8871	£1,462.27	0.0824	**£17,737.53**	n/a	n/a	66%	95%
	UC	£735.35	0.8047							
2 years	Dysport 1000U	£3,015.88	0.8976	£2,280.53	0.0923	£24,694.44	£433.53	n/a	19%	74%
	UC	£735.35	0.8052							
BOTOX										
2 years	BOTOX	£3,578.82	0.8677	£2,843.47	0.0250	£113,806.38	£2,343.77	£2,093.92	0%	0%
	UC	£735.35	0.8427							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

© NICE 2023. All rights reserved. Subject to Notice of rights.

SA7/8: Shaw/BoTULS data on repeat, 25-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

This was the same as SA1/2 but with a 25-week interval between injection cycles applied based on ULIS III observational study (Turner-Stokes 2021)[31]. Results are presented in Table 15 and Table 16.

When a 1-year time horizon was explored, where the proportion receiving repeat injections was taken/extrapolated from BoTULS (Shaw 2010),[27] up to a total of 3 injection cycles over 1 year, Dysport (500U) was cost-effective compared to usual care but only without the usual care arm and those who did not have repeats receiving twice annual follow up neurology consultant-led multidisciplinary attendances (£19,870 per QALY, 49% probability cost effective). When neurology attendances were included, Dysport (500U and 1000U) are cost-effective compared to usual care (ICERs, £12,577 and £18,657 per QALY respectively). Using the PAS price for Xeomin, Xeomin 250U wrist was cost effective but only with neurology attendances included (SA8). BOTOX had the highest ICER.

When a 2-year horizon was explored, with a total of up to 5 injection cycles over 2 years, the following are cost effective at a threshold of £20,000 per QALY compared to usual care Dysport (500U and 1000U) both with and without the usual care arm and those who did not have repeats receiving twice annual follow up neurology consultant-led multidisciplinary attendances. Using PAS prices for Xeomin, Xeomin 250U wrist (with and without attendances), Xeomin 400U wrist (with attendances) and Xeomin 250U elbow (with attendances) were cost effective. BOTOX had the highest ICER and was not cost effective in any scenario.

When a 5-year horizon was explored, with a total of up to 11 injection cycles over 5 years the following are cost effective at a threshold of £20,000 per QALY compared to usual care Xeomin (250U wrist and 400U wrist, with PAS price) and Dysport (500U and 1000U) both with and without the usual care arm and those who did not have repeats receiving twice annual follow up neurology consultant-led multidisciplinary attendances. In addition, with the PAS price for Xeomin, Xeomin 250U elbow (SA7, SA8), 250U and 400U finger (SA8) and 400U elbow (SA8) were cost effective at £20,000 per QALY. BOTOX had the highest ICER and was not cost effective in any scenario.

Table 15: Probabilistic results SA7 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£1,227.56	0.4588	£1,227.56	0.0415	£29,557.15	£396.92	n/a	8%	49%
	UC	£0.00	0.4172							
2 years	Xeomin 250U	£1,711.43	0.9020	£1,711.43	0.0817	£20,958.33	£78.26	n/a	41%	83%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£0.00	0.8204							
5 years	Xeomin 250U	£2,732.07	2.1439	£2,732.07	0.1941	**£14,076.96**	n/a	n/a	82%	97%
	UC	£0.00	1.9498							
1 year	Xeomin 400U	£1,675.26	0.4623	£1,675.26	0.0334	£50,169.70	£1,007.42	£673.50	0%	2%
	UC	£0.00	0.4289							
2 years	Xeomin 400U	£2,344.15	0.9089	£2,344.15	0.0657	£35,704.37	£1,031.06	£374.52	1%	27%
	UC	£0.00	0.8433							
5 years	Xeomin 400U	£3,761.21	2.1602	£3,761.21	0.1560	£24,103.75	£640.36	n/a	26%	72%
	UC	£0.00	2.0042							
Dysport										
1 year	Dysport 500U	£836.99	0.4512	£836.99	0.0421	**£19,870.03**	n/a	n/a	49%	90%
	UC	£0.00	0.4091							
2 years	Dysport 500U	£1,159.42	0.8871	£1,159.42	0.0828	**£13,998.89**	n/a	n/a	87%	99%
	UC	£0.00	0.8043							
5 years	Dysport 500U	£1,839.51	2.1084	£1,839.51	0.1968	**£9,344.93**	n/a	n/a	99%	100%
	UC	£0.00	1.9115							
1 year	Dysport 1000U	£1,190.65	0.4560	£1,190.65	0.0470	£25,344.71	£251.09	n/a	16%	72%
	UC	£0.00	0.4090							
2 years	Dysport 1000U	£1,659.24	0.8966	£1,659.24	0.0924	**£17,963.33**	n/a	n/a	65%	94%
	UC	£0.00	0.8042							
5 years	Dysport 1000U	£2,651.94	2.1309	£2,651.94	0.2195	**£12,079.91**	n/a	n/a	93%	99%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£0.00	1.9113							
BOTOX										
1 year	BOTOX	£1,433.08	0.4410	£1,433.08	0.0127	£113,284.49	£1,180.07	£1,053.57	0%	0%
	UC	£0.00	0.4283							
2 years	BOTOX	£2,001.91	0.8670	£2,001.91	0.0249	£80,486.14	£1,504.46	£1,255.73	0%	0%
	UC	£0.00	0.8422							
5 years	BOTOX	£3,201.74	2.0607	£3,201.74	0.0591	£54,160.62	£2,019.43	£1,428.27	0%	0%
	UC	£0.00	2.0016							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

Table 16: Probabilistic results SA8 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£1,293.46	0.4581	£919.46	0.0411	£22,374.85	£97.59	n/a	32%	79%
	UC	£374.00	0.4170							
2 years	Xeomin 250U	£1,869.14	0.9006	£1,133.79	0.0808	**£14,032.50**	n/a	n/a	83%	97%
	UC	£735.35	0.8198							
5 years	Xeomin 250U	£3,212.42	2.1405	£1,464.68	0.1920	**£7,627.23**	n/a	n/a	99%	100%
	UC	£1,747.73	1.9485							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
1 year	Xeomin 400U	£1,740.10	0.4631	£1,366.10	0.0337	£40,506.17	£691.58	£354.33	0%	14%
	UC	£374.00	0.4293							
2 years	Xeomin 400U	£2,500.95	0.9105	£1,765.60	0.0663	£26,626.11	£439.38	n/a	16%	61%
	UC	£735.35	0.8441							
5 years	Xeomin 400U	£4,233.59	2.1639	£2,485.86	0.1576	£15,772.97	n/a	n/a	73%	95%
	UC	£1,747.73	2.0063							
Dysport										
1 year	Dysport 500U	£903.19	0.4508	£529.19	0.0419	**£12,636.42**	n/a	n/a	93%	99%
	UC	£374.00	0.4090							
2 years	Dysport 500U	£1,317.61	0.8865	£582.26	0.0823	**£7,071.38**	n/a	n/a	100%	100%
	UC	£735.35	0.8041							
5 years	Dysport 500U	£2,319.15	2.1068	£571.42	0.1957	**£2,919.85**	n/a	n/a	100%	100%
	UC	£1,747.73	1.9111							
1 year	Dysport 1000U	£1,256.02	0.4564	£882.02	0.0470	**£18,759.65**	n/a	n/a	58%	94%
	UC	£374.00	0.4094							
2 years	Dysport 1000U	£1,816.63	0.8974	£1,081.28	0.0924	**£11,696.68**	n/a	n/a	95%	99%
	UC	£735.35	0.8049							
5 years	Dysport 1000U	£3,125.99	2.1328	£1,378.26	0.2197	**£6,272.99**	n/a	n/a	100%	100%
	UC	£1,747.73	1.9131							
BOTOX										
1 year	BOTOX	£1,498.83	0.4409	£1,124.83	0.0126	£88,948.68	£871.91	£745.45	0%	0%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£374.00	0.4282							
2 years	BOTOX	£2,159.36	0.8668	£1,424.01	0.0249	£57,272.15	£926.73	£678.09	0%	1%
	UC	£735.35	0.8420							
5 years	BOTOX	£3,682.46	2.0603	£1,934.73	0.0591	£32,739.45	£752.83	£161.89	0%	0%
	UC	£1,747.73	2.0012							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA9/10: Shaw/BoTULS data on repeat, 14-week interval between repeats +/- neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

This was the same as SA1/2 but with a 14-week interval between injection cycles applied based on Turner-Stokes 2013[30] and Kanovsky 2011[11]. Results are presented in Table 17 and Table 18.

When a 1-year time horizon was explored, where the proportion receiving repeat injections was taken from BoTULS (Shaw 2010),[27] up to a total of 4 injection cycles over 1 year, only Dysport (500U) compared to usual care was cost effective (ICER: £17,719 per QALY, probability cost effective 66%) 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 (SA10).

When a 2-year horizon was explored, with a total of up to 8 injection cycles over 2 years the following are cost effective at a threshold of £20,000 per QALY compared to usual care Dysport (500U) in those who did not have neurology attendances (SA9, ICER: £18,959 per QALY) and the following in SA10 where neurology attendances are included: Xeomin 250U (when PAS prise was applied), Dysport 500U and 1000U (ICERs: £13,781 per QALY and £19,932 per QALY respectively). BOTOX had the highest ICER and was not cost effective.

When a 5-year horizon was explored, with a total of up to 19 injection cycles over 5 years the following are cost effective at a threshold of £20,000 per QALY compared to usual care Xeomin 250U wrist (with PAS price applied) and Dysport 500U and 1000U both with and without the usual care arm and those who did not have repeats received twice annual follow up neurology consultant-led multidisciplinary attendances. Of note, with PAS

© NICE 2023. All rights reserved. Subject to Notice of rights.

prices for Xeomin applied, in SA10, with neurology attendances included, the ICER for Xeomin 400U wrist was just over the £20,000 per QALY threshold. In addition Xeomin 250U elbow was cost effective. BOTOX had the highest ICER and was not cost effective in any scenario.

Table 17: Probabilistic results SA9 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£1,489.98	0.4588	£1,489.98	0.0415	£35,884.46	£659.55	£244.33	1%	26%
	UC	£0.00	0.4173							
2 years	Xeomin 250U	£2,312.03	0.9021	£2,312.03	0.0816	£28,320.08	£679.25	n/a	11%	54%
	UC	£0.00	0.8205							
5 years	Xeomin 250U	£3,808.34	2.1442	£3,808.34	0.1940	**£19,627.18**	n/a	n/a	49%	87%
	UC	£0.00	1.9501							
1 year	Xeomin 400U	£2,034.78	0.4628	£2,034.78	0.0337	£60,311.98	£1,360.03	£1,022.65	0%	0%
	UC	£0.00	0.4291							
2 years	Xeomin 400U	£3,166.19	0.9100	£3,166.19	0.0663	£47,730.76	£1,839.50	£1,176.16	0%	4%
	UC	£0.00	0.8436							
5 years	Xeomin 400U	£5,217.90	2.1627	£5,217.90	0.1577	£33,096.15	£2,064.72	£488.13	4%	36%
	UC	£0.00	2.0051							
Dysport										
1 year	Dysport 500U	£1,011.86	0.4509	£1,011.86	0.0418	£24,184.77	£175.08	n/a	22%	77%
	UC	£0.00	0.4090							
2 years	Dysport 500U	£1,559.62	0.8865	£1,559.62	0.0823	**£18,959.12**	n/a	n/a	57%	92%
	UC	£0.00	0.8043							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
5 years	Dysport 500U	£2,556.67	2.1070	£2,556.67	0.1955	**£13,076.62**	n/a	n/a	91%	99%
	UC	£0.00	1.9115							
1 year	Dysport 1000U	£1,442.51	0.4565	£1,442.51	0.0474	£30,439.06	£494.71	£20.81	3%	46%
	UC	£0.00	0.4092							
2 years	Dysport 1000U	£2,235.11	0.8976	£2,235.11	0.0932	£23,987.54	£371.55	n/a	23%	77%
	UC	£0.00	0.8045							
5 years	Dysport 1000U	£3,672.40	2.1335	£3,672.40	0.2215	**£16,582.83**	n/a	n/a	73%	97%
	UC	£0.00	1.9120							
BOTOX										
1 year	BOTOX	£1,741.58	0.4409	£1,741.58	0.0127	£137,462.55	£1,488.19	£1,361.49	0%	0%
	UC	£0.00	0.4283							
2 years	BOTOX	£2,707.95	0.8669	£2,707.95	0.0249	£108,707.37	£2,209.74	£1,960.64	0%	0%
	UC	£0.00	0.8420							
5 years	BOTOX	£4,466.98	2.0605	£4,466.98	0.0592	£75,448.82	£3,282.87	£2,690.82	0%	0%
	UC	£0.00	2.0013							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

Table 18: Probabilistic results SA10 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£1,603.29	0.4589	£1,229.29	0.0417	£29,459.96	£394.74	n/a	8%	50%
	UC	£374.00	0.4172							
2 years	Xeomin 250U	£2,636.03	0.9023	£1,900.68	0.0820	£23,166.51	£259.79	n/a	29%	75%
	UC	£735.35	0.8202							
5 years	Xeomin 250U	£4,782.35	2.1444	£3,034.62	0.1950	**£15,562.44**	n/a	n/a	73%	95%
	UC	£1,747.73	1.9494							
1 year	Xeomin 400U	£2,149.25	0.4626	£1,775.25	0.0332	£53,439.26	£1,110.85	£778.65	0%	1%
	UC	£374.00	0.4294							
2 years	Xeomin 400U	£3,496.22	0.9096	£2,760.87	0.0653	£42,269.01	£1,454.53	£801.37	0%	10%
	UC	£735.35	0.8443							
5 years	Xeomin 400U	£6,214.07	2.1619	£4,466.33	0.1552	£28,770.59	£1,361.54	n/a	10%	54%
	UC	£1,747.73	2.0066							
Dysport										
1 year	Dysport 500U	£1,124.71	0.4513	£750.71	0.0424	**£17,719.00**	n/a	n/a	66%	95%
	UC	£374.00	0.4089							
2 years	Dysport 500U	£1,883.35	0.8874	£1,148.00	0.0833	**£13,781.17**	n/a	n/a	89%	99%
	UC	£735.35	0.8041							
5 years	Dysport 500U	£3,532.31	2.1090	£1,784.58	0.1980	**£9,013.68**	n/a	n/a	99%	100%
	UC	£1,747.73	1.9110							
1 year	Dysport 1000U	£1,556.23	0.4564	£1,182.23	0.0466	£25,349.59	£249.49	n/a	15%	72%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£374.00	0.4098							
2 years	Dysport 1000U	£2,563.03	0.8974	£1,827.68	0.0917	**£19,931.73**	n/a	n/a	51%	90%
	UC	£735.35	0.8057							
5 years	Dysport 1000U	£4,663.16	2.1330	£2,915.43	0.2179	**£13,377.31**	n/a	n/a	89%	98%
	UC	£1,747.73	1.9150							
BOTOX										
1 year	BOTOX	£1,855.13	0.4410	£1,481.13	0.0127	£116,577.57	£1,227.03	£1,099.98	0%	0%
	UC	£374.00	0.4283							
2 years	BOTOX	£3,032.10	0.8671	£2,296.74	0.0250	£91,941.14	£1,797.13	£1,547.33	0%	0%
	UC	£735.35	0.8422							
5 years	BOTOX	£5,440.13	2.0610	£3,692.40	0.0594	£62,190.95	£2,504.96	£1,911.24	0%	0%
	UC	£1,747.73	2.0016							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA11: Shaw/BoTULS repeats rate of repeats applied to MAS responder RCT data, 12-week interval between repeats, with neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

In this analysis the proportion receiving repeat injections was estimated by applying the rate from BoTULS (Shaw 2010)[27] , including the extrapolation with trendline, to the highest proportion of MAS responders from each RCT informing the model, a 12-week interval was applied and neurology attendances were included.

At 1 year, none of the BoNT-A were cost effective at £20,000 per QALY. At 2 years, only Dysport 500U was cost effective (ICER: £17,003 per QALY, probability cost effective 71%). At 5 years, Xeomin 250U wrist (with and without PAS price) and Dysport 500U (ICER £12,040 per QALY,

© NICE 2023. All rights reserved. Subject to Notice of rights.

probability cost effective 94%) and Dysport 1000U (ICER £17, 854 per QALY, probability cost effective 66%) were cost effective. Xeomin 400U wrist and BOTOX were not cost effective at any time horizon. All results reported in Table 19.

Table 19: Probabilistic results SA11 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£1,916.89	0.4583	£1,542.89	0.0413	£37,330.63	£716.28	£302.98	1%	21%
	UC	£374.00	0.4170							
2 years	Xeomin 250U	£2,922.39	0.9012	£2,187.03	0.0813	£26,912.93	£561.77	n/a	13%	61%
	UC	£735.35	0.8199							
5 years	Xeomin 250U	£5,420.75	2.1419	£3,673.02	0.1931	**£19,017.30**	n/a	n/a	53%	89%
	UC	£1,747.73	1.9487							
1 year	Xeomin 400U	£2,815.87	0.4632	£2,441.87	0.0339	£72,073.70	£1,764.27	£1,425.47	0%	0%
	UC	£374.00	0.4293							
2 years	Xeomin 400U	£4,286.96	0.9107	£3,551.61	0.0666	£53,315.71	£2,219.32	£1,553.17	0%	1%
	UC	£735.35	0.8441							
5 years	Xeomin 400U	£7,796.33	2.1646	£6,048.59	0.1583	£38,203.69	£2,882.10	£1,298.85	0%	19%
	UC	£1,747.73	2.0063							
Dysport										
1 year	Dysport 500U	£1,384.89	0.4517	£1,010.89	0.0424	£23,863.90	£163.68	n/a	22%	78%
	UC	£374.00	0.4093							
2 years	Dysport 500U	£2,151.51	0.8881	£1,416.16	0.0833	**£17,002.98**	n/a	n/a	71%	95%
	UC	£735.35	0.8048							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
5 years	Dysport 500U	£4,131.18	2.1107	£2,383.45	0.1980	**£12,040.36**	n/a	n/a	94%	99%
	UC	£1,747.73	1.9128							
1 year	Dysport 1000U	£1,987.43	0.4569	£1,613.43	0.0471	£34,284.09	£672.22	£201.61	0%	29%
	UC	£374.00	0.4098							
2 years	Dysport 1000U	£3,050.64	0.8983	£2,315.28	0.0925	£25,022.08	£464.69	n/a	17%	74%
	UC	£735.35	0.8058							
5 years	Dysport 1000U	£5,674.32	2.1350	£3,926.59	0.2199	**£17,854.82**	n/a	n/a	66%	95%
	UC	£1,747.73	1.9151							
BOTOX										
1 year	BOTOX	£1,933.76	0.4410	£1,559.76	0.0127	£123,110.49	£1,306.37	£1,179.67	0%	0%
	UC	£374.00	0.4284							
2 years	BOTOX	£2,891.00	0.8671	£2,155.64	0.0249	£86,534.63	£1,657.43	£1,408.32	0%	0%
	UC	£735.35	0.8422							
5 years	BOTOX	£5,284.57	2.0610	£3,536.84	0.0592	£59,737.72	£2,352.72	£1,760.65	0%	0%
	UC	£1,747.73	2.0017							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

SA12: Shaw/BoTULS repeats rate of repeats applied to MAS responder RCT data, 25-week interval between repeats, with neurology attendances for usual care / those not receiving repeat injections (1-, 2- and 5-year horizon)

© NICE 2023. All rights reserved. Subject to Notice of rights.

In this analysis the proportion receiving repeat injections was estimated by applying the rate from BoTULS (Shaw 2010)[27] , including the extrapolation with trendline, to the highest proportion of MAS responders from each RCT informing the model, a 25-week interval was applied and neurology attendances were included.

At 1 year, Xeomin 250U wrist (only with PAS price applied) and Dysport 500U are cost effective (ICER £13,300 per QALY). At 2 years, Xeomin 250U wrist (with and without PAS price) and Dysport (500U and 1000U) were cost effective (ICERs: £7,673 and £13,246 per QALY, respectively). At 5 years, Xeomin (250U and 400U, wrist, with and without PAS price applied) and Dysport (500U and 1000U) were cost effective (ICERs: £3,403 and £7,521 per QALY, respectively). BOTOX was not cost effective at any time horizon. The results are reported in Table 20.

Table 20: Probabilistic results SA12 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (wrist)										
1 year	Xeomin 250U	£1,309.14	0.4586	£935.14	0.0417	£22,419.84	£100.93	n/a	33%	78%
	UC	£374.00	0.4169							
2 years	Xeomin 250U	£1,896.34	0.9017	£1,160.99	0.0820	**£14,156.55**	n/a	n/a	82%	97%
	UC	£735.35	0.8196							
5 years	Xeomin 250U	£3,261.68	2.1430	£1,513.95	0.1949	**£7,767.15**	n/a	n/a	99%	100%
	UC	£1,747.73	1.9481							
1 year	Xeomin 400U	£1,904.00	0.4630	£1,530.00	0.0335	£45,637.02	£859.49	£524.24	0%	6%
	UC	£374.00	0.4294							
2 years	Xeomin 400U	£2,785.04	0.9103	£2,049.68	0.0659	£31,094.87	£731.34	£72.17	5%	42%
	UC	£735.35	0.8444							
5 years	Xeomin 400U	£4,771.38	2.1635	£3,023.65	0.1567	**£19,299.89**	n/a	n/a	52%	88%
	UC	£1,747.73	2.0069							
Dysport										
1 year	Dysport 500U	£933.17	0.4508	£559.17	0.0420	**£13,300.36**	n/a	n/a	91%	99%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£374.00	0.4087							
2 years	Dysport 500U	£1,369.62	0.8863	£634.26	0.0827	**£7,672.96**	n/a	n/a	99%	100%
	UC	£735.35	0.8036							
5 years	Dysport 500U	£2,416.35	2.1064	£668.62	0.1965	**£3,403.23**	n/a	n/a	100%	100%
	UC	£1,747.73	1.9099							
1 year	Dysport 1000U	£1,341.98	0.4563	£967.98	0.0472	£20,492.02	£23.24	n/a	44%	90%
	UC	£374.00	0.4090							
2 years	Dysport 1000U	£1,965.60	0.8971	£1,230.25	0.0929	**£13,246.08**	n/a	n/a	92%	99%
	UC	£735.35	0.8042							
5 years	Dysport 1000U	£3,407.92	2.1322	£1,660.19	0.2207	**£7,520.96**	n/a	n/a	100%	100%
	UC	£1,747.73	1.9115							
BOTOX										
1 year	BOTOX	£1,357.54	0.4415	£983.54	0.0126	£77,951.19	£731.19	£605.02	0%	0%
	UC	£374.00	0.4289							
2 years	BOTOX	£1,914.28	0.8681	£1,178.92	0.0248	£47,521.96	£682.76	£434.68	0%	3%
	UC	£735.35	0.8433							
5 years	BOTOX	£3,215.25	2.0632	£1,467.52	0.0590	£24,889.31	£288.28	n/a	0%	0%
	UC	£1,747.73	2.0042							

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 250U and 400U Masakado 2020,[15] Dysport 500U and Dysport 1000U (Gracies 2015)[8], BOTOX (Wein 2018)[33]).

© NICE 2023. All rights reserved. Subject to Notice of rights.

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:

- Up to 1000U Dysport or up to 400U Xeomin used for upper limb spasticity
- Proportion receiving repeat injections decreases over time (repeats given based on an assessment of need)

The results are driven by higher proportion of responders in Dysport and Xeomin trials and lower costs of Dysport and Xeomin (with PAS price applied).

When longer intervals between injection cycles (25 weeks) are explored Xeomin 400U was cost effective when the proportion receiving repeat injections decreases over time. A 14-week interval produced similar results to the basecase 12 week interval, however, in SA10 with neurology attendances included, the ICER for Xeomin 400U wrist (with PAS cost applied) was just over the £20,000 per QALY threshold.

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 at shorter time horizons. This is less of a concern at a 5-year time horizon.

This analysis is based on single RCTs (no meta-analysis possible) and not all indications reported here (upper and lower limb for each drug). 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. There was some heterogeneity between the RCTs included in this model, such as trial population age and time since stroke, these differences may account for differences in the proportion of responders observed both in the placebo and intervention arms.

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.

Although sensitivity analyses were conducted to explore the impact of longer intervals between repeat injections (14-weeks and 25-weeks), there remains uncertainty as to whether the QALY benefit would be maintained over longer intervals of 25 weeks due to a lack of RCT evidence.

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[14] 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,[14] Australian preference weights were applied. Finally, Kanovsky 2009[12] was an RCT in

© NICE 2023. All rights reserved. Subject to Notice of rights.

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[26] 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 £41,120 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 £82,363 per QALY over 5 years (SA1). 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 (SA3/4) 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 Dysport (up to 1000U) and Xeomin (250U) may be 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[13] 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)[26] 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:

- Up to 1000U Dysport or up to 400U Xeomin used for upper limb spasticity
- Proportion receiving repeat injections decreases over time (repeats given based on an assessment of need)

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

include a protocol where participants are provided with repeat injections following an assessment of need.

© NICE 2023. All rights reserved. Subject to Notice of rights.

References

1. Abogunrin S, Hortobagyi L, Remak E, Dinet J, Gabriel S, Bakheit AM. Budget impact analysis of botulinum toxin A therapy for upper limb spasticity in the United Kingdom. Clinicoeconomics & Outcomes Research. 2015; 7:185-193

2. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from: https://www.evidence.nhs.uk/formulary/bnf/current Last accessed: 04 April 2017.

3. Brashear A, Gordon MF, Elovic E, Kassicieh VD, Marciniak C, Do M et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. New England Journal of Medicine. 2002; 347(6):395-400

4. Danchenko N, Johnston KM, Whalen J. The cost-effectiveness of abobotulinumtoxinA (Dysport) and onabotulinumtoxinA (Botox) for managing spasticity of the upper and lower limbs, and cervical dystonia. Journal of Medical Economics. 2022; 25(1):919-929

5. Doan QV, Gillard P, Brashear A, Halperin M, Hayward E, Varon S et al. Cost-effectiveness of onabotulinumtoxinA for the treatment of wrist and hand disability due to upper-limb post-stroke spasticity in Scotland. European Journal of Neurology. 2013; 20(5):773-780

6. Elovic EP, Munin MC, Kanovsky P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. Muscle and Nerve. 2016; 53(3):415-421

7. Esquenazi A, Wein TH, Ward AB, Geis C, Liu C, Dimitrova R. Optimal Muscle Selection for OnabotulinumtoxinA Injections in Poststroke Lower-Limb Spasticity: A Randomized Trial. American Journal of Physical Medicine and Rehabilitation. 2019; 98(5):360-368

8. Gracies JM, Brashear A, Jech R, McAllister P, Banach M, Valkovic P et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. Lancet Neurology. 2015; 14(10):992-1001

9. Hansen RN, Lubinga SJ, Fonseca T, Dinet J, Gabriel S, Sullivan SD. Mapping the Modified Ashworth Scale and Physician’s Global Assessment to Preference-Based Health Utilities in Adults with Lower Limb Spasticity. Value in Health. 2017; 20(9):A727

10. Johnston KM, Danchenko N, Lundkvist J. PND34 resource use related to cervical dystonia, pediatric lower limb spasticity and adult upper limb spasticity in the united kingdom: A physician questionnaire. Value in Health. 2020; 23:S265

11. Kanovsky P, Slawek J, Denes Z, Platz T, Comes G, Grafe S et al. Efficacy and safety of treatment with incobotulinum toxin A (botulinum neurotoxin type A free from complexing proteins; NT 201) in post-stroke upper limb spasticity. Journal of Rehabilitation Medicine. 2011; 43(6):486-492

12. Kanovsky P, Slawek J, Denes Z, Platz T, Sassin I, Comes G et al. Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity. Clinical Neuropharmacology. 2009; 32(5):259-265

© NICE 2023. All rights reserved. Subject to Notice of rights.

13. Lindsay C, Humphreys I, Phillips C, Pandyan A. Estimating the cost consequence of the early use of botulinum toxin in post-stroke spasticity: Secondary analysis of a randomised controlled trial. Clinical Rehabilitation. 2022;

14. Makino K, Tilden D, Guarnieri C, Mudge M, Baguley IJ. Cost Effectiveness of Long-Term Incobotulinumtoxin-A Treatment in the Management of Post-stroke Spasticity of the Upper Limb from the Australian Payer Perspective. PharmacoEconomics Open. 2019; 3(1):93-102

15. Masakado Y, Abo M, Kondo K, Saeki S, Saitoh E, Dekundy A et al. Efficacy and safety of incobotulinumtoxinA in post-stroke upper-limb spasticity in Japanese subjects: results from a randomized, double-blind, placebo-controlled study (J-PURE). Journal of Neurology. 2020; 267(7):2029-2041

16. National institute for Health and Care Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine: Technology appraisal guidance [TA260]. London. 2012. Available from: https://www.nice.org.uk/guidance/ta260/

17. National institute for Health and Care Excellence. Cannabis-based medicinal products: NICE Guideline [NG144]. London. 2019. Available from: https://www.nice.org.uk/guidance/ng144

18. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20

19. National Institute for Health and Care Excellence. The NICE Charter. 2020. Available from: https://www.nice.org.uk/about/who-we-are/our-charter Last accessed: 01/05/2023.

20. National Institute for Health and Clinical Excellence. Social value judgements: principles for the development of NICE guidance. London. National Institute for Health and Clinical Excellence, 2008. Available from: https://www.nice.org.uk/media/default/about/what-we-do/research-and-development/social-value-judgements-principles-for-the-development-of-nice-guidance.pdf

21. NHS England and NHS Improvement. 2019/20 National Cost Collection Data Publication. 2022. Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication Last accessed: 01/02/2023.

22. NHS England and NHS Improvement. National Cost Collection Data Publication 2019-2020. London. 2020. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/06/National-Cost-Collection-2019-20-Report-FINAL.pdf

23. Peacock JL, Sauzet O, Ewings SM, Kerry SM. Dichotomising continuous data while retaining statistical power using a distributional approach. Statistics in Medicine. 2012; 31(26):3089-3103

24. Rosales RL, Kong KH, Goh KJ, Kumthornthip W, Mok VC, Delgado-De Los Santos MM et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. Neurorehabilitation and Neural Repair. 2012; 26(7):812-821

25. Royal College of Physicians. Spasticity in adults: management using botulinum toxin. London. 2018. Available from: http://www.rcplondon.ac.uk/guidelines-policy/spasticity-adults-management-using-botulinum-toxin

© NICE 2023. All rights reserved. Subject to Notice of rights.

26. Shackley P, Shaw L, Price C, van Wijck F, Barnes M, Graham L et al. Cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A: results from the Botulinum Toxin for the Upper Limb after Stroke (BoTULS) trial. Toxins. 2012; 4(12):1415-1426

27. Shaw L, Rodgers H, Price C, van Wijck F, Shackley P, Steen N et al. BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. Health Technology Assessment. 2010; 14(25):1-142

28. Tao W, Yan D, Li JH, Shi ZH. Gait improvement by low-dose botulinum toxin A injection treatment of the lower limbs in subacute stroke patients. Journal of Physical Therapy Science. 2015; 27(3):759-762

29. Turcu-Stiolica A, Subtirelu MS, Bumbea AM. Can Incobotulinumtoxin-A Treatment Improve Quality of Life Better Than Conventional Therapy in Spastic Muscle Post-Stroke Patients? Results from a Pilot Study from a Single Center. Brain Sciences. 2021; 11(7):15

30. Turner-Stokes L, Fheodoroff K, Jacinto J, Maisonobe P. Results from the Upper Limb International Spasticity Study-II (ULISII):a large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management. BMJ Open. 2013; 3(6)

31. Turner-Stokes L, Jacinto J, Fheodoroff K, Brashear A, Maisonobe P, Lysandropoulos A et al. Longitudinal goal attainment with integrated upper limb spasticity management including repeat injections of botulinum toxin A: Findings from the prospective, observational Upper Limb International Spasticity (ULIS-III) cohort study. Journal of Rehabilitation Medicine. 2021; 53(2):jrm00157

32. van Exel NJ, Scholte op Reimer WJ, Koopmanschap MA. Assessment of post-stroke quality of life in cost-effectiveness studies: the usefulness of the Barthel Index and the EuroQoL-5D. Quality of Life Research. 2004; 13(2):427-433

33. Wallace AC, Talelli P, Crook L, Austin D, Farrell R, Hoad D et al. Exploratory Randomized Double-Blind Placebo-Controlled Trial of Botulinum Therapy on Grasp Release After Stroke (PrOMBiS). Neurorehabilitation and Neural Repair. 2020; 34(1):51-60

34. Ward A, Roberts G, Warner J, Gillard S. Cost-effectiveness of botulinum toxin type a in the treatment of post-stroke spasticity. Journal of Rehabilitation Medicine. 2005; 37(4):252-257

35. Wein T, Esquenazi A, Jost WH, Ward AB, Pan G, Dimitrova R. OnabotulinumtoxinA for the Treatment of Poststroke Distal Lower Limb Spasticity: A Randomized Trial. Pm & R. 2018; 10(7):693-703

© NICE 2023. All rights reserved. Subject to Notice of rights.

Appendix A: Additional results

Results for other clinical target patterns for Xeomin are reported below.

Table 21: Probabilistic results SA1 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
12 week	Xeomin 250U	£568.75	0.1004	£568.75	0.0046	£124,813.55	£477.61	£432.05	0%	0%
	UC	£0.00	0.0958							
1 year	Xeomin 250U	£1,728.14	0.4350	£1,728.14	0.0197	£87,518.17	£1,333.22	£1,135.76	0%	0%
	UC	£0.00	0.4153							
2 years	Xeomin 250U	£2,495.88	0.8553	£2,495.88	0.0388	£64,286.17	£1,719.39	£1,331.14	0%	1%
	UC	£0.00	0.8165							
5 years	Xeomin 250U	£4,163.16	2.0328	£4,163.16	0.0923	£45,116.75	£2,317.65	£1,394.90	1%	13%
	UC	£0.00	1.9406							
12 week	Xeomin 400U	£763.60	0.1034	£763.60	0.0073	£105,224.20	£618.46	£545.89	0%	0%
	UC	£0.00	0.0961							
1 year	Xeomin 400U	£2,369.81	0.4479	£2,369.81	0.0314	£75,360.12	£1,740.88	£1,426.42	0%	0%
	UC	£0.00	0.4164							
2 years	Xeomin 400U	£3,433.58	0.8806	£3,433.58	0.0618	£55,532.90	£2,196.98	£1,578.69	0%	1%
	UC	£0.00	0.8188							
5 years	Xeomin 400U	£5,745.75	2.0930	£5,745.75	0.1470	£39,099.52	£2,806.71	£1,337.19	1%	17%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£0.00	1.9461							
Xeomin (elbow)										
12 week	Xeomin 250U	£568.75	0.1009	£568.75	0.0058	£98,543.06	£453.32	£395.60	0%	0%
	UC	£0.00	0.0951							
1 year	Xeomin 250U	£1,727.93	0.4373	£1,727.93	0.0250	£69,089.00	£1,227.73	£977.62	0%	0%
	UC	£0.00	0.4123							
2 years	Xeomin 250U	£2,494.99	0.8598	£2,494.99	0.0492	£50,737.20	£1,511.49	£1,019.74	0%	5%
	UC	£0.00	0.8106							
5 years	Xeomin 250U	£4,157.71	2.0435	£4,157.71	0.1169	£35,574.07	£1,820.21	£651.47	4%	29%
	UC	£0.00	1.9267							
12 week	Xeomin 400U	£763.60	0.1017	£763.60	0.0066	£116,295.01	£632.28	£566.62	0%	0%
	UC	£0.00	0.0952							
1 year	Xeomin 400U	£2,362.59	0.4409	£2,362.59	0.0285	£83,034.90	£1,793.53	£1,509.00	0%	0%
	UC	£0.00	0.4124							
2 years	Xeomin 400U	£3,416.09	0.8669	£3,416.09	0.0559	£61,063.09	£2,297.22	£1,737.78	0%	0%
	UC	£0.00	0.8109							
5 years	Xeomin 400U	£5,701.60	2.0604	£5,701.60	0.1330	£42,881.16	£3,042.34	£1,712.72	0%	11%
	UC	£0.00	1.9274							

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Table 22: Probabilistic results SA2 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
12 week	Xeomin 250U	£568.75	0.1004	£568.75	0.0045	£126,027.58	£478.49	£433.36	0%	0%
	UC	£0.00	0.0959							
1 year	Xeomin 250U	£1,890.87	0.4350	£1,516.87	0.0196	£77,565.86	£1,125.75	£930.19	0%	0%
	UC	£374.00	0.4155							
2 years	Xeomin 250U	£2,879.45	0.8554	£2,144.09	0.0385	£55,762.43	£1,375.08	£990.58	0%	4%
	UC	£735.35	0.8169							
5 years	Xeomin 250U	£5,339.25	2.0330	£3,591.52	0.0914	£39,300.43	£1,763.79	£849.93	3%	23%
	UC	£1,747.73	1.9416							
12 week	Xeomin 400U	£763.60	0.1034	£763.60	0.0073	£104,491.00	£617.44	£544.37	0%	0%
	UC	£0.00	0.0961							
1 year	Xeomin 400U	£2,525.43	0.4482	£2,151.43	0.0317	£67,938.83	£1,518.09	£1,201.41	0%	0%
	UC	£374.00	0.4165							
2 years	Xeomin 400U	£3,804.16	0.8812	£3,068.81	0.0623	£49,287.46	£1,823.54	£1,200.90	0%	3%
	UC	£735.35	0.8189							
5 years	Xeomin 400U	£6,898.27	2.0943	£5,150.54	0.1480	£34,804.88	£2,190.87	£711.04	2%	30%
	UC	£1,747.73	1.9463							
Xeomin (elbow)										
12 week	Xeomin 250U	£568.75	0.1008	£568.75	0.0058	£98,375.59	£453.12	£395.31	0%	0%
	UC	£0.00	0.0950							
1 year	Xeomin 250U	£1,891.16	0.4369	£1,517.16	0.0251	£60,558.44	£1,016.10	£765.57	0%	1%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£374.00	0.4118							
2 years	Xeomin 250U	£2,881.10	0.8589	£2,145.75	0.0493	£43,561.10	£1,160.58	£668.00	0%	12%
	UC	£735.35	0.8097							
5 years	Xeomin 250U	£5,345.36	2.0415	£3,597.62	0.1171	£30,729.57	£1,256.15	£85.41	9%	44%
	UC	£1,747.73	1.9244							
12 week	Xeomin 400U	£763.60	0.1016	£763.60	0.0066	£115,075.17	£630.89	£564.53	0%	0%
	UC	£0.00	0.0950							
1 year	Xeomin 400U	£2,527.25	0.4405	£2,153.25	0.0288	£74,883.80	£1,578.16	£1,290.61	0%	0%
	UC	£374.00	0.4117							
2 years	Xeomin 400U	£3,807.59	0.8660	£3,072.24	0.0565	£54,340.66	£1,941.51	£1,376.14	0%	1%
	UC	£735.35	0.8095							
5 years	Xeomin 400U	£6,904.35	2.0583	£5,156.62	0.1344	£38,375.66	£2,469.18	£1,125.46	1%	19%
	UC	£1,747.73	1.9239							

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.

Table 23: Probabilistic results SA3 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
1 year	Xeomin 250U	£2,615.75	0.4348	£2,615.75	0.0197	£133,051.10	£2,222.56	£2,025.96	0%	0%
	UC	£0.00	0.4152							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
2 years	Xeomin 250U	£4,593.53	0.8550	£4,593.53	0.0387	£118,835.04	£3,820.43	£3,433.89	0%	0%
	UC	£0.00	0.8163							
1 year	Xeomin 400U	£3,590.00	0.4480	£3,590.00	0.0316	£113,699.83	£2,958.51	£2,642.77	0%	0%
	UC	£0.00	0.4164							
2 years	Xeomin 400U	£6,320.82	0.8808	£6,320.82	0.0621	£101,815.71	£5,079.20	£4,458.39	0%	0%
	UC	£0.00	0.8187							
Xeomin (elbow)										
1 year	Xeomin 250U	£2,615.75	0.4375	£2,615.75	0.0250	£104,498.72	£2,115.12	£1,864.81	0%	0%
	UC	£0.00	0.4125							
2 years	Xeomin 250U	£4,593.53	0.8602	£4,593.53	0.0492	£93,333.39	£3,609.20	£3,117.04	0%	0%
	UC	£0.00	0.8110							
1 year	Xeomin 400U	£3,590.00	0.4407	£3,590.00	0.0286	£125,597.28	£3,018.33	£2,732.50	0%	0%
	UC	£0.00	0.4121							
2 years	Xeomin 400U	£6,320.82	0.8665	£6,320.82	0.0562	£112,469.62	£5,196.82	£4,634.81	0%	0%
	UC	£0.00	0.8103							

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Table 24: Probabilistic results SA4 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
1 year	Xeomin 250U	£2,615.75	0.4348	£2,241.75	0.0198	£113,330.86	£1,846.14	£1,648.33	0%	0%
	UC	£374.00	0.4150							
2 years	Xeomin 250U	£4,593.53	0.8549	£3,858.18	0.0389	£99,201.65	£3,080.33	£2,691.41	0%	0%
	UC	£735.35	0.8160							
1 year	Xeomin 400U	£3,590.00	0.4483	£3,216.00	0.0315	£102,079.07	£2,585.90	£2,270.85	0%	0%
	UC	£374.00	0.4168							
2 years	Xeomin 400U	£6,320.82	0.8814	£5,585.47	0.0619	£90,168.79	£4,346.58	£3,727.13	0%	0%
	UC	£735.35	0.8194							
Xeomin (elbow)										
1 year	Xeomin 250U	£2,615.75	0.4372	£2,241.75	0.0250	£89,687.32	£1,741.85	£1,491.89	0%	0%
	UC	£374.00	0.4122							
2 years	Xeomin 250U	£4,593.53	0.8595	£3,858.18	0.0491	£78,505.80	£2,875.27	£2,383.82	0%	0%
	UC	£735.35	0.8104							
1 year	Xeomin 400U	£3,590.00	0.4405	£3,216.00	0.0287	£112,027.15	£2,641.85	£2,354.78	0%	0%
	UC	£374.00	0.4118							
2 years	Xeomin 400U	£6,320.82	0.8662	£5,585.47	0.0564	£98,956.15	£4,456.59	£3,892.15	0%	0%
	UC	£735.35	0.8098							

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Table 25: Probabilistic results SA5 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
2 years	Xeomin 250U	£2,762.77	0.8558	£2,762.77	0.0383	£72,216.30	£1,997.63	£1,615.06	0%	1%
	UC	£0.00	0.8175							
2 years	Xeomin 400U	£3,804.01	0.8795	£3,804.01	0.0617	£61,673.13	£2,570.41	£1,953.60	0%	0%
	UC	£0.00	0.8178							
Xeomin (elbow)										
2 years	Xeomin 250U	£2,768.53	0.8593	£2,768.53	0.0488	£56,745.99	£1,792.77	£1,304.89	0%	2%
	UC	£0.00	0.8105							
2 years	Xeomin 400U	£3,793.69	0.8657	£3,793.69	0.0559	£67,862.37	£2,675.64	£2,116.61	0%	0%
	UC	£0.00	0.8097							

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.

Table 26: Probabilistic results SA6 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
2 years	Xeomin 250U	£3,101.54	0.8565	£2,366.18	0.0391	£60,563.84	£1,584.80	£1,194.11	0%	2%
	UC	£735.35	0.8174							
2 years	Xeomin 400U	£4,137.53	0.8819	£3,402.18	0.0620	£54,852.12	£2,161.69	£1,541.44	0%	1%
	UC	£735.35	0.8199							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (elbow)										
2 years	Xeomin 250U	£3,105.63	0.8589	£2,370.28	0.0495	£47,914.24	£1,380.90	£886.20	0%	7%
	UC	£735.35	0.8094							
2 years	Xeomin 400U	£4,135.21	0.8667	£3,399.86	0.0565	£60,219.12	£2,270.70	£1,706.11	0%	0%
	UC	£735.35	0.8103							

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.

Table 27: Probabilistic results SA7 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
1 year	Xeomin 250U	£1,227.96	0.4351	£1,227.96	0.0197	£62,301.82	£833.76	£636.67	0%	1%
	UC	£0.00	0.4154							
2 years	Xeomin 250U	£1,713.35	0.8555	£1,713.35	0.0388	£44,211.76	£938.29	£550.75	1%	14%
	UC	£0.00	0.8167							
5 years	Xeomin 250U	£2,739.58	2.0333	£2,739.58	0.0921	£29,743.83	£897.46	n/a	14%	48%
	UC	£0.00	1.9412							
1 year	Xeomin 400U	£1,671.65	0.4474	£1,671.65	0.0313	£53,357.97	£1,045.07	£731.78	0%	1%
	UC	£0.00	0.4161							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
2 years	Xeomin 400U	£2,338.07	0.8797	£2,338.07	0.0616	£37,956.64	£1,106.10	£490.12	0%	18%
	UC	£0.00	0.8181							
5 years	Xeomin 400U	£3,746.71	2.0908	£3,746.71	0.1464	£25,591.87	£818.66	n/a	18%	69%
	UC	£0.00	1.9444							
Xeomin (elbow)										
1 year	Xeomin 250U	£1,228.08	0.4366	£1,228.08	0.0252	£48,720.32	£723.95	£471.88	0%	6%
	UC	£0.00	0.4114							
2 years	Xeomin 250U	£1,712.58	0.8585	£1,712.58	0.0496	£34,554.82	£721.35	£225.74	4%	32%
	UC	£0.00	0.8089							
5 years	Xeomin 250U	£2,734.47	2.0403	£2,734.47	0.1178	£23,214.14	£378.60	n/a	31%	71%
	UC	£0.00	1.9225							
1 year	Xeomin 400U	£1,673.25	0.4403	£1,673.25	0.0287	£58,260.12	£1,098.84	£811.64	0%	0%
	UC	£0.00	0.4115							
2 years	Xeomin 400U	£2,339.88	0.8656	£2,339.88	0.0565	£41,436.29	£1,210.49	£645.80	0%	11%
	UC	£0.00	0.8092							
5 years	Xeomin 400U	£3,747.98	2.0574	£3,747.98	0.1342	£27,925.73	£1,063.73	n/a	11%	57%
	UC	£0.00	1.9232							

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.

© NICE 2023. All rights reserved. Subject to Notice of rights.

Table 28: Probabilistic results SA8 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
1 year	Xeomin 250U	£1,293.15	0.4351	£919.15	0.0198	£46,315.85	£522.25	£323.79	1%	11%
	UC	£374.00	0.4153							
2 years	Xeomin 250U	£1,868.77	0.8556	£1,133.42	0.0390	£29,047.50	£353.03	n/a	15%	50%
	UC	£735.35	0.8165							
5 years	Xeomin 250U	£3,209.89	2.0334	£1,462.15	0.0927	£15,766.40	n/a	n/a	66%	88%
	UC	£1,747.73	1.9407							
1 year	Xeomin 400U	£1,741.96	0.4477	£1,367.96	0.0315	£43,488.43	£738.84	£424.29	0%	8%
	UC	£374.00	0.4163							
2 years	Xeomin 400U	£2,504.73	0.8803	£1,769.38	0.0618	£28,608.65	£532.42	-£86.05	9%	54%
	UC	£735.35	0.8184							
5 years	Xeomin 400U	£4,239.21	2.0922	£2,491.48	0.1470	**£16,949.42**	-£448.42	-£1,918.37	68%	94%
	UC	£1,747.73	1.9452							
Xeomin (elbow)										
1 year	Xeomin 250U	£1,295.34	0.4366	£921.34	0.0250	£36,911.19	£422.12	£172.51	3%	26%
	UC	£374.00	0.4116							
2 years	Xeomin 250U	£1,871.98	0.8584	£1,136.62	0.0491	£23,159.54	£155.06	n/a	32%	71%
	UC	£735.35	0.8093							
5 years	Xeomin 250U	£3,213.03	2.0401	£1,465.30	0.1166	**£12,562.04**	n/a	n/a	83%	96%
	UC	£1,747.73	1.9234							
1 year	Xeomin 400U	£1,739.50	0.4402	£1,365.50	0.0289	£47,319.61	£788.36	£499.79	0%	4%

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
	UC	£374.00	0.4113							
2 years	Xeomin 400U	£2,499.08	0.8655	£1,763.73	0.0567	£31,085.48	£628.97	£61.59	5%	43%
	UC	£735.35	0.8088							
5 years	Xeomin 400U	£4,228.81	2.0570	£2,481.08	0.1349	**£18,398.73**	n/a	n/a	58%	90%
	UC	£1,747.73	1.9222							

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.

Table 29: Probabilistic results SA9 (no neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										
1 year	Xeomin 250U	£1,489.14	0.4350	£1,489.14	0.0196	£75,909.98	£1,096.80	£900.62	0%	0%
	UC	£0.00	0.4153							
2 years	Xeomin 250U	£2,310.04	0.8552	£2,310.04	0.0386	£59,890.59	£1,538.62	£1,152.91	0%	3%
	UC	£0.00	0.8166							
5 years	Xeomin 250U	£3,801.92	2.0326	£3,801.92	0.0917	£41,472.77	£1,968.47	£1,051.74	2%	20%
	UC	£0.00	1.9409							
1 year	Xeomin 400U	£2,040.38	0.4470	£2,040.38	0.0313	£65,246.96	£1,414.95	£1,102.23	0%	0%
	UC	£0.00	0.4157							
2 years	Xeomin 400U	£3,179.65	0.8789	£3,179.65	0.0615	£51,713.41	£1,949.93	£1,335.07	0%	2%
	UC	£0.00	0.8174							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
5 years	Xeomin 400U	£5,246.82	2.0889	£5,246.82	0.1461	£35,903.87	£2,324.11	£862.76	2%	26%
	UC	£0.00	1.9427							
Xeomin (elbow)										
1 year	Xeomin 250U	£1,490.44	0.4373	£1,490.44	0.0255	£58,515.73	£981.02	£726.32	0%	1%
	UC	£0.00	0.4118							
2 years	Xeomin 250U	£2,313.04	0.8598	£2,313.04	0.0501	£46,186.71	£1,311.43	£810.63	0%	8%
	UC	£0.00	0.8097							
5 years	Xeomin 250U	£3,807.87	2.0434	£3,807.87	0.1190	£31,991.77	£1,427.34	£237.07	7%	40%
	UC	£0.00	1.9244							
1 year	Xeomin 400U	£2,038.83	0.4401	£2,038.83	0.0281	£72,667.39	£1,477.69	£1,197.12	0%	0%
	UC	£0.00	0.4120							
2 years	Xeomin 400U	£3,177.09	0.8653	£3,177.09	0.0552	£57,592.45	£2,073.79	£1,522.14	0%	1%
	UC	£0.00	0.8101							
5 years	Xeomin 400U	£5,248.13	2.0565	£5,248.13	0.1311	£40,027.77	£2,625.89	£1,314.76	1%	15%
	UC	£0.00	1.9254							

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.

Table 30: Probabilistic results SA10 (neurology attendances for usual care/those not receiving repeats)

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
Xeomin (finger)										

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
1 year	Xeomin 250U	£1,601.41	0.4354	£1,227.41	0.0198	£61,964.14	£831.24	£633.16	0%	2%
	UC	£374.00	0.4156							
2 years	Xeomin 250U	£2,634.40	0.8561	£1,899.05	0.0389	£48,759.94	£1,120.11	£730.64	0%	8%
	UC	£735.35	0.8171							
5 years	Xeomin 250U	£4,784.76	2.0347	£3,037.03	0.0926	£32,809.22	£1,185.70	£260.04	8%	38%
	UC	£1,747.73	1.9421							
1 year	Xeomin 400U	£2,146.42	0.4477	£1,772.42	0.0313	£56,630.66	£1,146.46	£833.48	0%	0%
	UC	£374.00	0.4164							
2 years	Xeomin 400U	£3,488.65	0.8803	£2,753.30	0.0615	£44,741.84	£1,522.55	£907.18	0%	6%
	UC	£735.35	0.8188							
5 years	Xeomin 400U	£6,197.53	2.0922	£4,449.80	0.1463	£30,424.37	£1,524.64	£62.07	6%	46%
	UC	£1,747.73	1.9460							
Xeomin (elbow)										
1 year	Xeomin 250U	£1,603.59	0.4368	£1,229.59	0.0250	£49,157.00	£729.32	£479.18	0%	5%
	UC	£374.00	0.4117							
2 years	Xeomin 250U	£2,636.83	0.8587	£1,901.47	0.0492	£38,662.66	£917.85	£426.04	1%	22%
	UC	£735.35	0.8096							
5 years	Xeomin 250U	£4,783.83	2.0410	£3,036.10	0.1169	£25,973.99	£698.30	-£470.60	22%	61%
	UC	£1,747.73	1.9241							
1 year	Xeomin 400U	£2,150.99	0.4403	£1,776.99	0.0288	£61,645.81	£1,200.47	£912.21	0%	0%
	UC	£374.00	0.4115							

© NICE 2023. All rights reserved. Subject to Notice of rights.

Time horizon	Intervention	Total costs	Total QALYs	Incr Cost	Incr QALYs	ICER	Threshold @£20K	Threshold @£30K	Probability CE @£20K	Probability CE @£30K
2 years	Xeomin 400U	£3,497.81	0.8657	£2,762.46	0.0567	£48,740.60	£1,628.92	£1,062.16	0%	3%
	UC	£735.35	0.8091							
5 years	Xeomin 400U	£6,219.04	2.0576	£4,471.30	0.1347	£33,193.28	£1,777.20	£430.15	3%	35%
	UC	£1,747.73	1.9229							

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

© NICE 2023. All rights reserved. Subject to Notice of rights.

© NICE 2023. All rights reserved. Subject to Notice of rights.