MODELLING LONG-TERM OUTCOMES AND RISK OF DEATH FOR PATIENTS WITH POST-STROKE SPASTICITY RECEIVING ABOBOTULINUMTOXINA TREATMENT AND REHABILITATION THERAPY

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Objective: Stroke is associated with a high risk of death and cardiovascular events. Rehabilitation therapy is critical for functional recovery, to reduce hospital readmissions, all-cause and cardiovascular mortality, and stroke recurrence (long-term outcomes). Post-stroke spasticity may prevent effective recovery by restricting mobility. AbobotulinumtoxinA is an adjunctive therapy to physical therapy for post-stroke spasticity, but its long-term effects are unknown. The objective was to model the long-term clinical and economic outcomes of abobotulinumtoxinA for post-stroke spasticity.

Methods: Effects of abobotulinumtoxinA on treating post-stroke spasticity and evidence linking functional outcomes with long-term outcomes were collected in a focused literature review. A model was developed to estimate health benefits on long-term outcomes, direct medical costs, life- and quality-adjusted life-years for abobotulinumtoxinA injections plus rehabilitation therapy compared with rehabilitation therapy alone, from a UK perspective over a 10-year time-period.

Results: AbobotulinumtoxinA+rehabilitation therapy led to a risk reduction of 8.8% for all-cause mortality, and an increase of 13% in life-years and 59% in quality-adjusted life-years compared with rehabilitation therapy alone. AbobotulinumtoxinA+rehabilitation therapy was considered cost-effective compared with rehabilitation therapy alone (incremental cost-effectiveness ratio: £24,602).

Conclusion: AbobotulinumtoxinA + rehabilitation therapy may improve long-term outcomes, including post-stroke survival, while being cost-effective for the treatment of post-stroke spasticity.

Key words: stroke; spasticity; abobotulinumtoxinA; rehabilitation; cost-effectiveness analysis; mortality; United Kingdom.

Accepted June 16, 2022; Epub ahead of print July 18, 2022

DOI: 10.2340/jrm.v54.2422

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STROKE is the second most common cause of death and disability in Europe; it affects more than 1 million inhabitants of Europe every year (1). In 2017, there were 9.53 million stroke survivors in Europe. A significant proportion of stroke survivors will experience recurrent stroke, with 5-year cumulative incidence rates ranging from 16% to 30% (2, 3). First-ever ischaemic stroke is also associated with an increased risk of major adverse cardiovascular (CV) events in the first year after a stroke (4–6). Projections show that with no effective prevention strategy, including secondary prevention, the burden of stroke will not decrease in the next decade and beyond (7). To reduce the risks of death, secondary stroke and secondary major CV events (i.e. acute coronary syndrome, myocardial infarction, incident coronary artery disease, incident heart failure or CV death), and to foster physical recovery, stroke rehabilitation guidelines recommend that patients should engage in aerobic physical activity sessions to tackle physical inactivity (8, 9).
Stroke survivors may encounter distinct barriers to physical activity. Notably, 25.3% of survivors develop post-stroke spasticity (PSS) over the first year after a stroke, and they may also experience motor weakness, altered perception and balance, and impaired cognition that would result in inability to participate in exercise programmes (8, 10, 11).

Spasticity describes involuntary muscle hyperactivity in the presence of central paresis (12). Spasticity is generally associated with 1 or more lesions involving both the pyramidal and extrapyramidal tracts (13). As a result, spasticity can be a source of pain, discomfort and deformities, and can be a major barrier to physical exercise (8).

Treatment of spasticity often involves a combination of physical and pharmacological interventions, which can improve physical function and reduce secondary complications. AbobotulinumtoxinA therapy (aboBoNT-A; Dysport®, Ipsen Pharma, Boulogne-Billancourt, France) is a well tolerated and effective treatment for PSS of the upper and lower limbs (14, 15) that improves rehabilitation outcomes (16, 17) and relieves pain (18). AboBoNT-A treatment is also effective in improving patients’ quality of life (19).

Patients generally experience rapid improvement with aboBoNT-A therapy, thus clinical trials are of short duration. Consequently, it is not known if treatment-related improvements in mobility could also contribute to lowering the risks of CV events and all-cause death.

To assess if aboBoNT-A injections could also have an impact on long-term outcomes, a 10-year survival model was developed that compares the effects of aboBoNT-A injections and rehabilitation therapy (aboBoNT-A + RT) with rehabilitation therapy (RT) alone.

**METHODS**

**Survival model structure**

An exploratory 3-state model was developed using Microsoft Excel (Microsoft Office 365, Redmond, WA, USA) to estimate long-term outcomes (all-cause mortality and subsequent CV events), direct medical costs, life-years and quality-adjusted life-years (QALYs) of 2 interventions in PSS: aboBoNT-A + RT and RT alone, with RT encompassing all interventions aimed at improving the physical functioning and mobility of post-stroke survivors with spasticity (e.g. general physiotherapy aimed at improving movement and balance, cardiorespiratory and resistance training, strength exercise, etc.). The modelling was performed from a UK payer perspective over a 10-year time-period. The incremental costs per QALYs gained, ICER (incremental cost-effectiveness ratio), of aboBoNT-A + RT vs RT alone was calculated.

No studies of aboBoNT-A have evaluated the impact of aboBoNT-A injections on all-cause death and CV event risks. Thus, a focused literature review (FLR) was performed to search for evidence, with 2 objectives. First, to quantify the effect of botulinum toxin A (BoNT-A) on measures of disability for patients with PSS. Secondly, to quantify the association between measures of disability and long-term outcomes, such as death and secondary CV events, in stroke survivors (see Supplementary methods).

Publications identified in the FLR are available in the Supplementary materials (Tables SV and SVI). Of the evidence identified in the FLR, the Functional Independence Measure (FIM) was the only functional outcome that allowed us to model the effect of aboBoNT-A injections on all-cause mortality. There was insufficient evidence to compute a link between other disability or functional outcomes and long-term outcomes. The effect of aboBoNT-A injections on FIM score was studied in a randomized controlled study, and the gain in FIM score after rehabilitation was associated with a reduction in the risk of all-cause mortality in stroke survivors (20–22). When applicable, summary effect(s) for functional and long-term outcomes were computed with meta-analyses, using the random effect model in R (R core Team, 2021) [The R Foundation for Statistical Computing, Vienna, Austria] and the metafor package (23) (Table SII).

All patients in the model were followed for adverse events, time in PSS, and long-term outcome health states and death. In both interventions, patients were assumed to continue treatment for the duration of the 10-year time-period. The time in each health state was derived from survival data for stroke survivors.

**Survival data**

Four publications were considered as sources of data for overall survival after the first stroke (24–27). Because it is well known that a significant proportion of stroke survivors develop spasticity symptoms after the first stroke, these studies were considered to be relevant for our modelled patient population. To build the model, it was assumed that base overall survival rates of stroke survivors were identical for patients with or without spasticity symptoms. Kaplan–Meier survival curves from all studies were digitalized with WebPlotDigitizer (28) and reconstructed with Weibull or Gompertz parametric models (Figs S1–S4). The best model was selected based on the Akaike and Bayesian information criteria, and visual inspection, according to best practice in extrapolation of survival data (29). In the base-case analysis, the extrapolated survival
data of post-stroke patients reported by Wolfe and colleagues was used (24).

Intervention-specific survival probabilities were computed based on modelled hazard ratios (HRs) derived from the evidence identified in the FLR, assuming that the proportional hazard condition would be met (calculations are detailed in the Supplementary methods). Probabilities of non-fatal recurrent stroke and CV events were derived from the literature (3, 30).

Utility, resource identification, quantification and valuation

In the base case, healthcare resource utilization data were based on a cost-utility analysis of aboBoNT-A for PSS (31) (Table I). This study was selected as the best source of data for our model, because it included healthcare resource utilization and quality of life (as utility value) data for patients with either lower- or upper-limb spasticity or both, while other studies focused on upper-limb spasticity (32–36). Hourly rates of community-based and hospital-based healthcare services were derived from Unit Costs of Health & Social Care 2020, funded by the National Institute for Health Research UK (37). Unit costs of inpatient and outpatient healthcare services were collected from the National Health Service (NHS) UK Cost Collection 2018/2019 (Table II). The aboBoNT-A injection schedule was derived from the UK label (Dysport®, Ipsen, retrieved from medicines.org.uk in July 2021). All costs and health benefits were discounted by 3.5%, according to the National Institute for Health and Care Excellence (NICE) guide to the methods of technology appraisal (9). In the model, patients in the aboBoNT-A + RT intervention were assumed to receive an injection every 12 weeks and to continue treatment for the entirety of the modelled time-period. Twelve weeks is the minimal interval between aboBoNT-A injections based on the Dysport® label (UK, April 2021), making it a conservative assumption for our model.

Sensitivity analyses

A 1-way deterministic sensitivity analysis (DSA) was conducted by altering data inputs for key model variables. A probabilistic sensitivity analysis (PSA) was also conducted, with distributions assigned to key model variables and utility scores, by random sampling (1000 iterations). Uncertainties associated with utility scores were described by the β distribution, while uncertainties associated with costs and healthcare resource utilization were described by the γ distribution. Standard error for parameters were retrieved from the Lazzaro study (31) or they were assigned an appropriate (10%) coefficient of variation on their point estimate (38) (Table SVIII).

A second deterministic sensitivity analysis was performed to assess the impact of resource utilization estimates on incremental costs and the ICER. In this analysis, resource utilization data reported by Ward and colleagues (based on the UK healthcare practice) were used instead of the estimates reported by Lazzaro and colleagues, the latter being more conservative from a cost perspective (31, 33). It was assumed that estimates reported by Ward and colleagues (Table SX), although restricted to upper-limb spasticity, could reflect the benefit of aboBoNT-A injections for the treatment of both upper- and lower-limb spasticity on resource utilization in UK clinical practice.

RESULTS

A review of the literature identified FIM score as an efficacy outcome that could be used to model the effect of aboBoNT-A injections on all-cause mortality in post-stroke patients treated for spasticity. Stroke survivors who reported greater improvement in FIM score during rehabilitation had lower risk of all-cause mortality during follow-up (summary effect HR per 1-point gain in FIM: 0.9626, 95% confidence interval (95% CI) 0.9245–1.0022) (21, 22). Patients treated with aboBoNT-A injections + RT showed greater improvement in FIM score than patients treated without aboBoNT-A injections (Table SII) (20).
The modelling results showed that the addition of aboBoNT-A injections to RT led to a reduction of 8.8% in the risk of all-cause mortality, and a relative increase of 12.8% in discounted life-years (Table III). The addition of aboBoNT-A injections to RT led to an increase of £42,328 in total costs over 10 years, including £9,520 for drug acquisition and £743 for drug administration. In the base-case scenario, incremental costs were driven by the increased number of hours of home care and RT for patients treated with aboBoNT-A injections compared with RT alone, as reported by Lazzaro and colleagues (31).

Although a small change in life-years in favour of aboBoNT-A + RT was observed, the change in QALYs was more substantial. Over the 10-year period, aboBoNT-A + RT led to more QALYs than RT alone (4.647 vs 2.926, respectively) (Table III).

Overall, the ICER of aboBoNT-A injections was £24,602 per QALY, which is below the current upper threshold of £30,000 to be considered a cost-effective use of resources in the UK.

All of the evaluated scenario analyses remained under £30,000 per QALY gained. One scenario (using resource utilization data published by Ward and colleagues) found aboBoNT-A + RT to be cost saving compared with RT alone (£168,274 vs £171,330, respectively); in this scenario, aboBoNT-A + RT was economically dominant (Table SXI) (33).

According to UK national guidelines, patients usually should be re-injected when spasticity symptoms start to reoccur (39). In a previous longitudinal study of upper-limb spasticity, the mean time interval between aboBoNT-A injections was 156.4 days (22.3 weeks) (40). In the model, 3 different aboBoNT-A regimens were tested, with aboBoNT-A injections every 12 weeks (3 months), 16 weeks (4 months) and 24 weeks (6 months). The price of an aboBoNT-A

### Table II. Estimates for cost parameters

| Parameter                                      | Estimate | Reference – assumption |
|------------------------------------------------|----------|------------------------|
| Cost of a toxin vial, £                         | 154      | Dysport®, UK, Ex-MAN (50) |
| Cost of a toxin vial, U                         | 500      |                        |
| Administration cost – outpatient setting, £/h   | 47.33    |                         |
| Administration cost – day hospital, £/h         | 49.67    | Hospital-based physiotherapist (mean cost of a specialist from bands 5, 6, 7) – calculated from Curtis et al., 2020 (37) |
| Health care services                            |          |                        |
| Follow-up visits, £/unit                       | 58.00    | One-time cost of outpatient physiotherapy – NHS costs 2018–19 (51) |
| Rehabilitation in day hospital, £/h            | 49.67    | Hospital-based physiotherapist (mean cost of a specialist from bands 5, 6, 7) – calculated from Curtis et al., 2020 (37) |
| Rehabilitation in outpatient or home setting, £/h | 47.33    | Community-based physiotherapist (mean cost of a specialist from bands 5, 6, 7) – calculated from Curtis et al., 2020 (37) |
| Home care, £/h                                 | 27.29    | Weighted mean cost of home care per h (£24 per weekday h, £30 per face-to-face per weekday h, £25 per day-time weekend, £30 per face-to-face per day-time weekend) – calculated from Curtis et al., 2020 (37) |
| Intrathecal pump set-up, £                     | 8,764.00 | One-time cost of insertion of intrathecal drug delivery device for treatment of neurological conditions, 19 years and over – calculated based on NHS costs 2018–19 (51) |
| Baclofen cost, £/mg                             | 0.28     | Mean price available in the UK (50) |
| Baclofen intrathecal cost, £/mg                 | 5.42     | Mean price available in the UK (50) |
| Gabapentin cost, £/mg                           | 0.06     | Mean price available in the UK (50) |
| Cost of a secondary stroke event, £             | 4,750.71 | Mean cost per hospitalization, stroke, NHS costs 2018–19 (51) |
| Cost of a CV event, £                           | 2,366.94 | Mean cost per hospitalization, actual or suspected myocardial infarction, NHS costs 2018–19 (51) |

### Table III. Results of the base-case scenario

| Category          | Parameter                      | AboBoNT-A | RT        | Absolute difference |
|-------------------|-------------------------------|-----------|-----------|---------------------|
| Life-years        | Intervention                  | 5.15      | 4.56      | 0.59                |
|                   | Recurrent stroke              | 0.06      | 0.06      | 0.00                |
|                   | CV event                      | 0.01      | 0.01      | 0.00                |
|                   | Total life-years              | 5.22      | 4.63      | 0.59                |
| Recurrent stroke  | Cumulative risk over 10 years, % | 42.7    | 43.7      | −1.1                |
| CV events         | Cumulative risk over 10 years | 4.9       | 5.0       | −0.1                |
| QALYs             | Intervention                  | 4.59      | 2.89      | 1.70                |
|                   | Recurrent stroke              | 0.05      | 0.03      | 0.01                |
|                   | CV event                      | 0.01      | 0.00      | 0.00                |
|                   | Total QALYs                   | 4.65      | 2.92      | 1.73                |
| Costs (£)         | AboBoNT-A acquisition         | 9520      | -         | -                   |
|                   | Administration                | 743       | -         | -                   |
|                   | AE related                    | 3         | -         | -                   |
|                   | RT                            | 39,498    | 7,867     | 31,631              |
|                   | Recurrent stroke – hospitalization | 1202   | 1112      | 90                  |
|                   | Recurrent stroke – rehabilitation | 377    | 78.54     | 298                 |
|                   | CV event – hospitalization    | 66        | 61.28     | 5                   |
|                   | CV event – rehabilitation     | 46        | 9.70      | 37                  |
|                   | Total costs                   | 51,458    | 9,129     | 42,329              |

aboBoNT-A + RT: abobotulinumtoxinA injections plus rehabilitation therapy; AE: adverse event; CV: cardiovascular; QALY: quality-adjusted life-year; RT: rehabilitation therapy.
vial remained unchanged. The ICER associated with each different dosing timing (12, 16 and 24 weeks) was £24,602, £23,110 and £21,618, respectively.

In the base-case scenario, we selected the study by Wolfe and colleagues, a registry study performed in the UK, to extrapolate the survival probabilities of stroke survivors with spasticity, while we also identified additional sources of data in the literature (24–27). Changing the source of overall survival data led to an increase in the ICER (range: £24,405–28,877) (Table SVII and Table SIX).

A DSA was conducted to determine the model parameters contributing the greatest uncertainty to the model results. The DSA of the base-case analysis showed that home care (i.e. number of hours and costs), base HR for all-cause mortality, effect of aboBoNT-A + RT (or RT alone) on the functional outcome, quality of life and the cost of an aboBoNT-A vial were the parameters with the greatest influence on the ICER (Table IV). In general, the ICER remained under the £30,000 threshold, except in the low value for aboBoNT-A + RT subsequent year(s) utility value (−1 SD from the point estimate) and the high value for the HR for all-cause mortality (upper bound of the 95% CI).

Joint parameter uncertainty was explored with a PSA. In the base-case analysis, the SD of healthcare resource use parameters (i.e. number of follow-up visits per year, hours of rehabilitation in day hospital per year, hours of RT in outpatient or home setting per year, and the number of hours of home care per year) was set to 10% of the deterministic mean reported by Lazzaro and colleagues (31). A cost-effectiveness acceptability curve was generated to illustrate the probability that each strategy is cost-effective at varying levels of willingness to pay (Fig. 1). The PSA demonstrated a 73% likelihood that aboBoNT-A + RT is cost-effective compared with RT alone at an ICER threshold of £30,000. The results of the PSA are also represented in the cost-effectiveness plane scatterplot in Fig. 2, which demonstrates the results of 1,000 simulations.

A second PSA analysis was performed to explore the uncertainty related to the variance of the model inputs. In this analysis, the SD parameter of the sampling distribution for the healthcare resource use parameters was considered to be equal to the deterministic mean. This analysis showed that the likelihood of aboBoNT-A + RT being considered to be cost-effective against RT alone at an ICER threshold of £30,000 was 68% (Figs S5 and S6).

**DISCUSSION**

This analysis found that aboBoNT-A + RT compared with RT alone could reduce the risk of all-cause mortality by 8.8%, which can be considered to be highly important by decision-makers and relevant to patients. This is the first study to quantify the possible survival gain associated with physical function improvement for people with PSS. In the elderly population, physical activity is associated with improved overall health (41),

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**Table IV. Results of the one-way deterministic sensitivity analysis (DSA)**

| Parameter | Low value | High value | Low result, £ | High result, £ |
|-----------|-----------|------------|---------------|---------------|
| Home care, aboBoNT-A + RT, h/year | Lower range (Lazzaro 2020) | Upper range (Lazzaro 2020) | 13,486 | 25,694 |
| AboBoNT-A + RT, subsequent year(s) utility | −1 SD | +1 SD | 31,900 | 20,022 |
| HR functional outcome, mortality | LB 95% CI | UB 95% CI | 23,009 | 31,447 |
| Rehabilitation – subsequent year(s) utility | −1 SD | +1 SD | 21,537 | 28,684 |
| RT – functional outcome effect | −1 SD | +1 SD | 21,611 | 28,491 |
| Home care, £/h | 75% | 125% | 21,488 | 27,717 |
| AboBoNT-A + RT, functional outcome effect | −1 SD | +1 SD | 28,035 | 22,446 |
| Rehabilitation in outpatient or home setting, aboBoNT-A + RT, h/year | 75% | 125% | 23,546 | 25,659 |
| AboBoNT-A + RT, first year utility | −1 SD | +1 SD | 25,654 | 23,633 |
| Mean dose per injection session, U | 75% | 125% | 22,758 | 24,602 |
| Rehabilitation in outpatient or home setting, £/h | 75% | 125% | 23,802 | 25,403 |
| Rehabilitation, first year utility | −1 SD | +1 SD | 23,944 | 25,298 |
| Home care, RT, h/year | Lower range (Lazzaro 2020) | Upper range (Lazzaro 2020) | 25,322 | 24,153 |
| Rehabilitation in day hospital, aboBoNT-A + RT, h/year | 75% | 125% | 24,044 | 25,161 |
| Rehabilitation in day hospital, £/h | 75% | 125% | 24,103 | 25,102 |
| Rehabilitation in outpatient or home setting, RT, h/year | 75% | 125% | 24,858 | 24,346 |
| Baclofen cost, £/mg | 75% | 125% | 24,379 | 24,826 |
| Follow-up visits, physiotherapist, aboBoNT-A + RT, per year | 75% | 125% | 24,449 | 24,756 |
| Administration cost – day hospital, £/h | 75% | 125% | 24,502 | 24,703 |
| Follow-up visits, physiotherapist, RT, per year | 75% | 125% | 24,684 | 24,521 |
| Follow-up visits, £/unit | 75% | 125% | 24,530 | 24,674 |
| Intrathecal pump set-up, £ | 75% | 125% | 24,667 | 24,538 |
| Rehabilitation in day hospital, RT, h/year | 75% | 125% | 24,661 | 24,544 |
| HR functional outcome – CV event | LB 95% CI | UB 95% CI | 24,556 | 24,660 |

aboBoNT-A + RT: abobotulinumtoxinA injections plus rehabilitation therapy; 95% CI: 95% confidence interval; CV: cardiovascular; HR: hazard ratio; LB: lower-bound; RT: rehabilitation therapy; SD: standard deviation; UB: upper-bound.
including lower risk of CV events (42). Benefits resulting from physical activity in healthy individuals are also relevant to stroke survivors (43), who experience increased risks of recurrent stroke (2, 3, 30) and major adverse CV events (4–6). Immobility, motor weakness, and altered perception and balance experienced by stroke survivors greatly hinder their ability to follow clinical recommendations to tackle physical inactivity (8). Spastic symptoms, which occur in a significant proportion of stroke survivors, further contribute to the barriers to physical exercise (19).

Here, we modelled the effect of aboBoNT-A injections on all-cause mortality using a functional or a disability outcome as a linking variable. Given the lack of long-term studies of aboBoNT-A injections for PSS, treatment effects were modelled based on 1 randomized clinical trial assessing the benefit of aboBoNT-A injections on FIM score in patients with PSS, and 2 studies reporting a statistically significant association between gain in FIM score after post-stroke rehabilitation and the risk of all-cause mortality (20–22).

The literature search identified only 1 study reporting healthcare resource utilization data in stroke survivors with either upper- or lower-limb spasticity (31). This cost-utility analysis was performed from the Italian National Health Service perspective, and found that combining aboBoNT-A injections with RT resulted in a higher number of QALYs gained than with RT alone (1.620 vs 1.150, respectively), and incremental cost-utility ratios of €12,341 and €23,600 for the Italian NHS and societal perspectives, respectively. These results are consistent with our finding of 1.71 QALYs gained and an ICER of £24,602 per QALY gained. Other pharmaco-economic studies have assessed the benefit of BoNT-A injections compared with best supportive care in adult upper-limb spasticity (31–36), but these also had short time-periods and did not attempt to quantify treatment effects on mortality or secondary CV events. However, most of these studies concluded that BoNT-A injections are a cost-effective treatment for PSS (31, 33, 34, 36).

Extensive sensitivity analyses consistently found aboBoNT-A injections to be cost-effective. In the probabilistic analysis, 73% of simulations found an ICER below £30,000. A scenario considering alternative sources of resource utilization data (32, 33) found lower...
utilization of day hospital, day centre or physiotherapist resources, such that aboBoNT-A was cost saving and associated with a negative ICER. In addition, our base-case scenario assumed that patients were treated with aboBoNT-A for 10 years, with injection intervals of 12 weeks, according to the Dysport® label. In UK clinical practice, patients may undergo aboBoNT-A therapy for shorter periods of time and with longer time intervals between injections (40), leading to a lower incremental cost in the current analysis. Consequently, costs associated with aboBoNT-A therapy are conservative and likely to be overestimated in the current model.

Although BoNT-A therapy has been shown to be cost-effective for the treatment of post-stroke patients with upper-limb spasticity (31–34), the results of the current study show that it could also have a benefit for all-cause mortality, while remaining cost-effective. However, this study has several limitations. First, extensive healthcare resource utilization and quality of life data representative of the UK clinical practice for post-stroke patients with spasticity, independently of the limb affected (upper or lower limb), were not available in the literature. Consequently, the current study relied on data from Lazzaro and colleagues (31), which were based on the Italian clinical setting. Secondly, this model used evidence produced in a single randomized clinical trial assessing the effect of aboBoNT-A injections on FIM score after rehabilitation (20). However, another study (non-randomized, thus not included in the model) found that BoNT-A injections had a positive effect on FIM score (44).

AboBoNT-A therapy improves rehabilitation outcomes on functional independence (16, 17, 19) in patients with PSS, and several studies have shown that BoNT-A injections can decrease the burden of care of long-term care residents treated for upper- and lower-limb spasticity (45–47). The current model assessed the impact of aboBoNT-A injections on all-cause mortality, using FIM score as a linking variable. BoNT-A injections are known to improve disability, physical functioning and mobility, and the Barthel Index or the 6-minute walk test are often used to assess and report these improvements (Table SV). Some of the outcomes used in BoNT-A studies are associated with long-term outcomes in stroke survivors or in elderly patients (Tables SIII and SIV). However, the way the evidence was reported in the literature did not enable us to use different outcomes from FIM score as linking variables to model the effect of aboBoNT-A injections on all-cause mortality or CV events.

**CONCLUSION**

This is the first model to suggest that aboBoNT-A therapy may have additional long-term benefits that are not captured in spasticity-focused trials. AboBoNT-A injections significantly improve limb spasticity and mobility, enabling patients to regain some level of functional independence, while also reducing pain and caregiver burden (18, 20, 45–47). Improving patient mobility is also important to lower the risk of deep vein thrombosis and pressure ulcers, which can lead to infections (48, 49). It is clear that enabling funding for repeated aboBoNT-A injections is important, and this is supported by the evidence of a large international study that demonstrated the benefit of repeated cycles of aboBoNT-A, over 2 years captured through personcentred goal attainment and standardized measures (40).

The long-term survival rates of stroke survivors with spasticity have not been captured and reported in the literature. Therefore, the model was built based on survival rates of stroke survivors, knowing that a substantial proportion of these patients will have spasticity. While we assumed that these rates would be comparable to those of patients with spasticity, we anticipate that patients with spasticity and mobility impairments will have a lower life expectancy. Since the current model is comparing 2 intervention schemes in the same patient population, we do not expect this limitation to significantly alter the conclusion of this exploratory model. On the contrary, we consider that the model may underestimate the putative benefits of aboBoNT-A on the survival rates of stroke survivors with spasticity.

This study advocates for the need to consider and capture the impact of aboBoNT-A injections on all-cause mortality and secondary events, such as CV events and recurrent stroke, which are prevalent in stroke survivors (4–6). The model did not explore other long-term outcomes, such as pain or the burden of caregivers, which are also relevant to patients, caregivers and payers. Moreover, the current study did not explore the impact of treatment adherence or treatment discontinuation on the long-term benefits of aboBoNT-A injections.

In conclusion, the evidence reported in the literature and the results of this exploratory analysis strongly support the observation that aboBoNT-A injections are an effective use of resources for the treatment of PSS, with the potential to improve long-term outcomes, such as post-stroke survival. Future research will be beneficial to further test and validate the results and hypotheses presented in this study.

**ACKNOWLEDGEMENTS**

**Competing interests**

The authors have no conflicts of interest to declare.
Outcomes for patients with post-stroke spasticity receiving aboBoNT-A and rehabilitation

Funding
This study was funded by Ipsen.

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