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## Introduction

- SMA is a debilitating condition that often results in death or the need for permanent ventilation before 2 years of age if untreated[1,2]
- SMA is associated with substantial costs,[3] including:
  - Direct costs: inpatient, outpatient, and emergency care; medications; medical devices and mobility aids; respiratory and ventilatory assistance; and transportation[4–6]
  - Indirect costs: loss of productivity, time spent caregiving, anxiety and stress related to caregiving, and changes in employment status for the caregiver[4–6]
- Three approved DMTs are currently available: nusinersen, an intrathecally administered ASO; risdiplam, an oral small-molecule drug; and onasemnogene abeparvovec, a one-time gene replacement therapy[7]
- DMTs have demonstrated safety and efficacy in clinical trials for patients with SMA,[8–16] and can reduce both direct and indirect expenses related to SMA[17]
- NBS enables early treatment for SMA, which leads to improved outcomes,[11–13] but several barriers exist to universal implementation of NBS
  - NBS programs have been launched in several countries worldwide, but implementation is inconsistent[18,19]
  - Financial, technical, organizational, and ethical constraints have been cited as reasons to forego or delay widespread implementation of NBS for SMA[18]

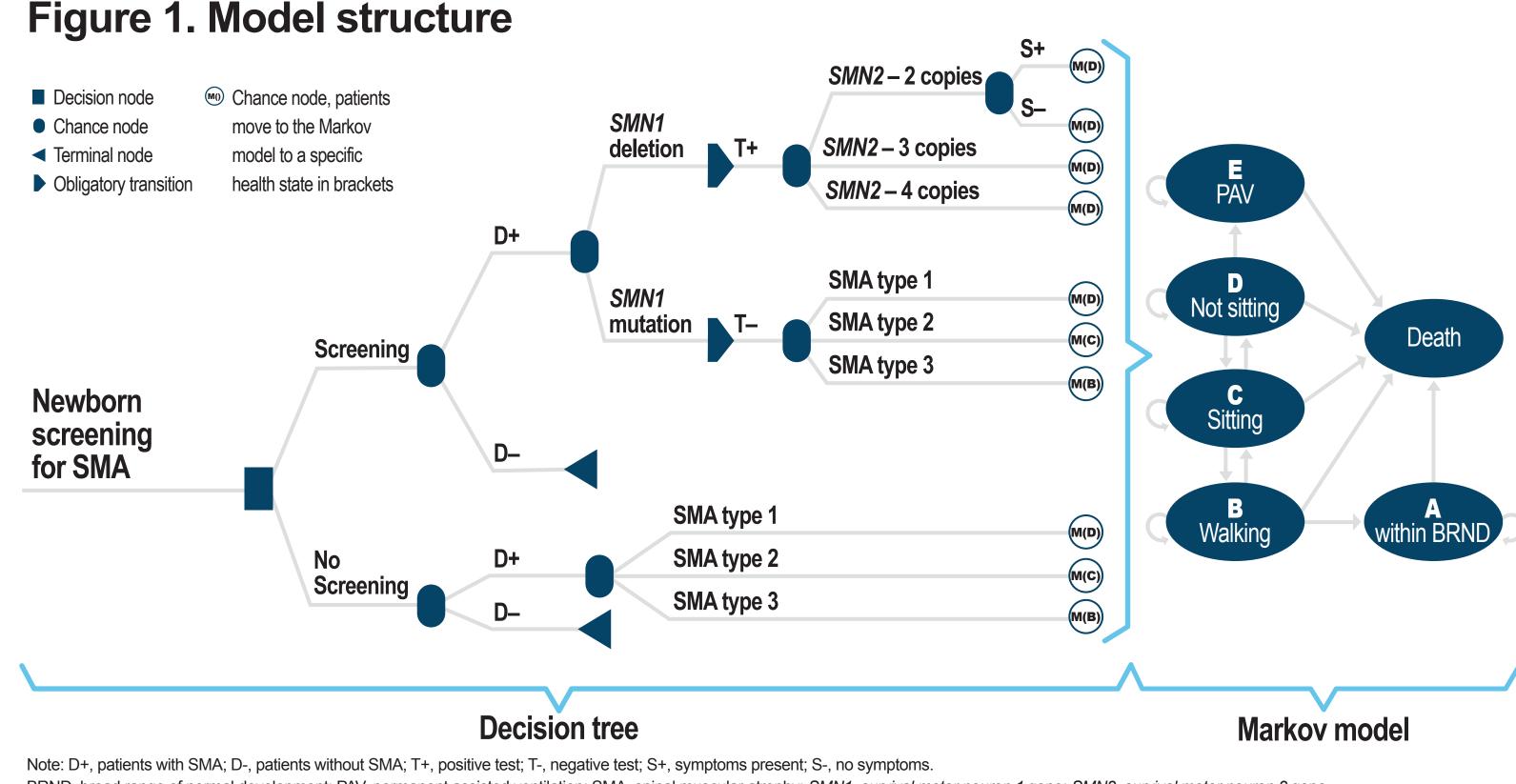## Objective

- We evaluated cost effectiveness of NBS followed by treatment compared with a treatment pathway without NBS for SMA to determine if NBS for SMA offers value for money in the health care system in England

## Methods

- A cost-utility analysis using a combination of decision tree and six-state Markov model structures was conducted to estimate the lifetime health effects and costs of NBS for SMA (patients identified with SMA who were either symptomatic or presymptomatic at time of screening) compared with non-NBS (patients with SMA who were symptomatic at diagnosis) from the perspective of the National Health Service (NHS) in England
- The decision tree captured NBS outcomes and costs, and the Markov modeling projected long-term health outcomes and costs following diagnosis (Figure 1)
- Patients in the model entered a specific Markov model health state (within a broad range of normal development [A], walking [B], sitting [C], not sitting [D], permanent assisted ventilation [E]) after the decision tree depending on SMA type or *SMN2* copy number
- In the base-case analysis, the model applied a lifetime time horizon from the perspective of NHS England and a discount rate of 3.5% for costs and outcomes[20]

### Figure 1. Model structure



Note: D+, patients with SMA; D–, patients without SMA; T+, positive test; T–, negative test; S+, symptoms present; S–, no symptoms.
BRND, broad range of normal development; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy; *SMN1*, survival motor neuron 1 gene; *SMN2*, survival motor neuron 2 gene.

- The following data and assumptions regarding survival, milestone achievements, and regressions were applied in the model:
  - Clinical data for presymptomatically and symptomatically treated patients were obtained from available relevant clinical trials for each treatment:
    - Onasemnogene abeparvovec: SPR1NT,[21] START,[22] STR1VE-US,[23] STR1VE-EU[24]
    - Nusinersen: NURTURE,[25] SHINE,[26] CS2/CS12[27]
    - Risdiplam: RAINBOWFISH,[28] FIREFISH[29]
  - Because SMA may be severe early in life or treatments may not be always instantly available after diagnosis, it is assumed that 40% of patients with two copies of *SMN2* identified via NBS become symptomatic before treatment initiation (LS interview, Nov/Dec 2021). Clinical outcomes for these patients are assumed to be poorer than for those patients with two copies of *SMN2* who are treated presymptomatically
  - For treated patients, the motor milestones achieved at the end of follow-up in the clinical trials were sustained for the patient's lifetime, and regression from a higher functioning health state to a worse functioning health state was not possible[30–33]
  - Untreated patients receiving best supportive care could lose their motor milestones of walking (i.e., transitioning from walking to sitting) and sitting (i.e., transitioning from sitting to non-sitting) based on observations from the natural history cohort[34]
  - Because of a lack of long-term survival data, retrospective chart reviews,[30] natural history studies,[31,32] and national life expectancy statistics[33] were used as proxies for survival
- Model inputs for patient distribution and treatment patterns were based on existing literature, local data, and expert opinion
  - The model included a total cohort of 585,195 newborns, based on the number of live births in England in 2020[35]
  - The SMA incidence was assumed to be 1 in 10,000[36–39]
  - SMA was caused by either homozygous gene deletion (96%) or point mutation (4%)[40]
  - Of cases detected presymptomatically, 45% of patients had two *SMN2* copies, 33% had three copies, and 22% had four copies[41,42]
  - Of cases detected after symptom onset, 58% of patients had SMA type 1, 29% had type 2, and 13% had type 3[43]
  - Based on expert opinion, the percentage of patients with SMA (detected before or after symptom onset) receiving each treatment (onasemnogene abeparvovec, nusinersen, risdiplam) by SMA type and copy number is presented in Table 1

### Table 1. Model inputs: percentage of patients receiving treatment for SMA

| | Onasemnogene abeparvovec | Nusinersen | Risdiplam | Best supportive care |
|---|---|---|---|---|
| **Patients detected presymptomatically, %** | | | | |
| Two *SMN2* copies | 93 | 6 | 0 | 1 |
| Three *SMN2* copies | 93 | 6 | 0 | 1 |
| Four *SMN2* copies | 0 | 6 | 50 | 44 |
| **Patients detected symptomatically, %** | | | | |
| SMA type 1 | 56 | 2 | 22 | 20 |
| SMA type 2 | 0 | 10 | 90 | 0 |
| SMA type 3 | 0 | 10 | 90 | 0 |
| **Patients identified via NBS but treated symptomatically, %** | | | | |
| Two *SMN2* copies | 93 | 6 | 0 | 1 |

NBS, newborn screening; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2 gene.

- The model included the following direct costs in the base-case analysis:
  - The cost of each heel-prick screening test (HPST) was assumed to be £4.54 (a Dutch value [which is in line with other sources in Europe] converted to GBP because of a lack of UK-specific data),[44] and the cost of each genetic test, which was used for confirmation after a positive HPST result, was assumed to be £1,200 (based on prices from Oxford Genetic Laboratories assuming both gene sequencing and multiplex ligation-dependent probe amplification were needed)[45]
  - Treatment and administration costs were based on UK list prices and the latest NHS reference costs (2019/2020)[46]
    - SMA care–related costs were based on an unpublished UK HCRU study and NICE's final draft guidance for SMA[47]
    - All cost were presented in 2021/2022 GBP values[48]
- To estimate the QALYs of patients identified with SMA, the following utility values were used:
  - State E: 0.00 (expert opinion)
  - State D: 0.19[49]
  - State C: 0.60[50]
  - States A and B: general population's health-related quality of life[51]
- Sensitivity and scenario analyses were conducted to assess the robustness of the model and the validity of the results
  - Indirect, caregiver, and transportation costs were applied in the societal perspective scenario

## Results

- NBS for SMA resulted in testing 585,195 newborns and identifying approximately 59 with SMA (96% of all SMA patients in England) (Table 2)

### Table 2. NBS Outcomes

| Outcome | NBS | Non-NBS |
|---|---|---|
| Number of tests performed | 585,254 | 58.5 |
| HPST (first tier) | 585,195 | 0 |
| Confirmatory genetic test (second tier) | 58.5 | 58.5 |
| **Number of cases identified and treated** | **58.5** | **58.5** |
| Presymptomatic | 46.2 | 0.0 |
| Symptomatic | 2.2 | 58.5 |

HPST, heel prick screening test; NBS, newborn screening.

- Base-case results indicated that NBS was dominant (less costly and more effective) compared with non-NBS
- NBS a cost saving of £67,238,145 and an estimated gain of 567 QALYs over the lifetime of a newborn cohort identified (approximately 59 patients) per year (Table 3)

### Table 3. Deterministic analysis results, base case (discounted)

| Strategy | Total costs | Total QALYs | Total QALYs | Incremental costs | Incremental LYs | Incremental QALYs | ICER (£ per QALY) |
|---|---|---|---|---|---|---|---|
| NBS | £154,927,491 | 1,381 | 1,177 | –£67,238,145 | 459 | 567 | Dominant |
| Non-NBS | £222,165,636 | 922 | 610 | | | | |

ICER, incremental cost-effectiveness ratio; LY, life-year; NBS, newborn screening; QALY, quality-adjusted life-year.

- Deterministic (Figure 2) and probabilistic sensitivity analyses (Table 4 and Figure 3) and scenario analyses (Table 5) demonstrated the robustness of the base-case results
  - All iterations of sensitivity and scenario analyses demonstrated that NBS is dominant (less costly and more effective) compared with non-NBS scenarios
  - In the probabilistic sensitivity analysis, NBS was associated with incremental costs of approximately –£65,366,421 and a gain of 556 QALYs (incremental costs and QALYs were mean values)
  - Scenario analyses demonstrated incremental costs of up to approximately –£111 million and gains of more than 1,987 QALYs

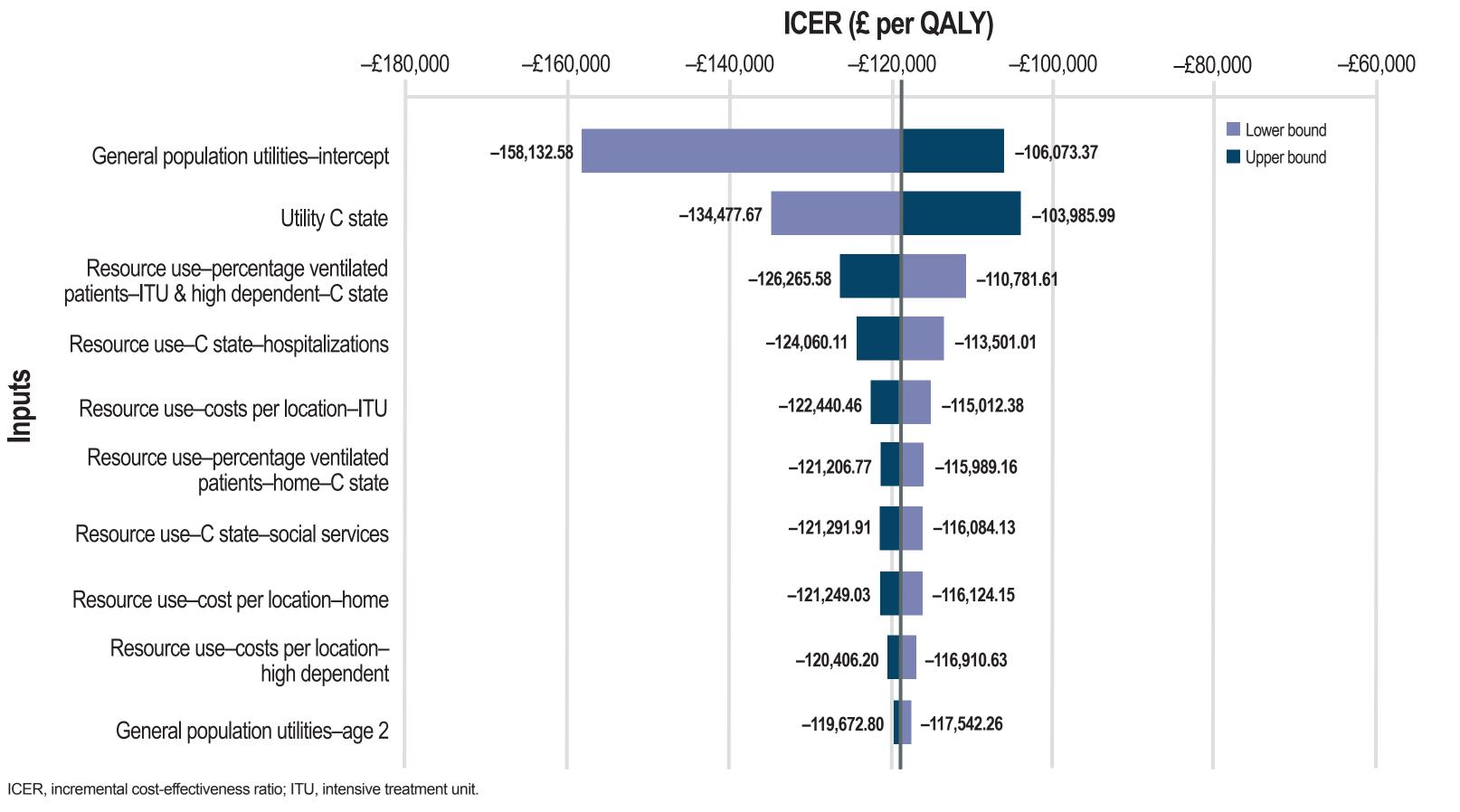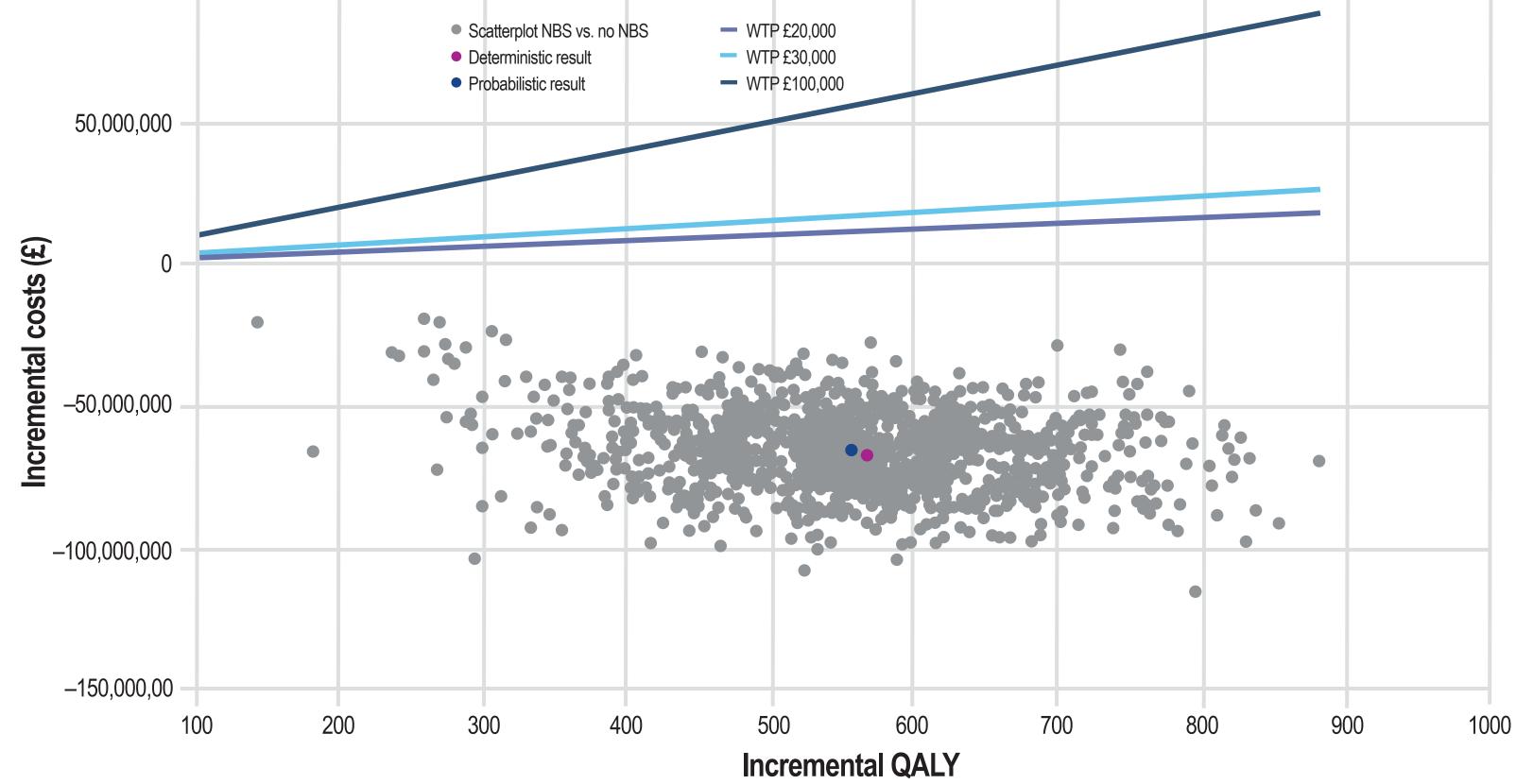### Figure 2. Tornado diagram for the deterministic sensitivity analysis



### Table 4. Mean probabilistic sensitivity analysis results (discounted)

| Strategy | Total costs | Total QALYs | Incremental costs | Incremental LYs | Incremental QALYs | ICER (£ per QALY) |
|---|---|---|---|---|---|---|
| NBS | £156,598,982 | 1,160 | –£65,366,421 | 556 | Dominant | Dominant |
| Non-NBS | £221,965,402 | 604 | | | | |

ICER, incremental cost-effectiveness ratio; LY, life-year; NBS, newborn screening; QALY, quality-adjusted life-year.

### Figure 3. Probabilistic sensitivity analysis results: incremental cost-effectiveness plane with willingness-to-pay thresholds



QALY, quality-adjusted life year; WTP, willingness-to-pay.

### Table 5. Scenario analysis results

| Strategy | Total costs (£) | Total LYs | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£ per QALY) |
|---|---|---|---|---|---|---|---|
| **Discount rate of 1.5%** | | | | | | | |
| NBS | £199,020,099 | 2,329 | 1,987 | –£110,852,776 | 987 | 1,071 | Dominant |
| Non-NBS | £309,872,875 | 1,343 | 916 | | | | |
| **Time horizon of 10 years** | | | | | | | |
| NBS | £110,806,003 | 456 | 349 | –£2,229,395 | 55 | 115 | Dominant |
| Non-NBS | £113,035,398 | 400 | 234 | | | | |
| **Time horizon of 50 years** | | | | | | | |
| NBS | £147,783,189 | 1,221 | 1,049 | –£64,861,802 | 345 | 473 | Dominant |
| Non-NBS | £212,644,991 | 876 | 575 | | | | |
| **C state survival based on Wijngaarde 2020[52]** | | | | | | | |
| NBS | £157,357,380 | 1,399 | 1,188 | –£113,636,088 | 248 | 441 | Dominant |
| Non-NBS | £270,993,468 | 1,151 | 748 | | | | |
| **Societal perspective** | | | | | | | |
| NBS | £161,343,572 | 1,381 | 1,177 | –£84,146,774 | 459 | 567 | Dominant |
| Non-NBS | £245,490,346 | 922 | 610 | | | | |

ICER, incremental cost-effectiveness ratio; LY, life-year; NBS, newborn screening; QALY, quality-adjusted life-year.

## Conclusions

- NBS for SMA in England is less costly, with a lifetime savings of £67,238,145, and more effective than a scenario without NBS
- Implementation of NBS followed by presymptomatic treatment results in improved health outcomes for patients with SMA in England
- Therefore, NBS is a cost-effective use of resources from the perspective of the NHS

### References

1. Verhaart IEC, et al. *Orphanet J Rare Dis.* 2017;12:124.
2. Lally C, et al. *Orphanet J Rare Dis.* 2017;12:175.
3. Dangouloff T, et al. *Orphanet J Rare Dis.* 2021;16:47.
4. Landfeldt E, et al. *Appl Health Econ Health Policy.* 2021;19:501–20.
5. McMillan HJ, et al. *J Neuromuscul Dis.* 2021;8:553–68.
6. Belter L, et al. *J Mark Access Health Policy.* 2020;8:1843277.
7. Ramdas S, et al. *Expert Opin. Pharmacother.* 2020;21:307–15.
8. Mendell JR, et al. *N Engl J Med.* 2017;377:1713–22.
9. Day JW, et al. *Lancet Neurol.* 2021;20:284–93.
10. Mercuri E, et al. *Lancet Neurol.* 2021;20:832–41.
11. Strauss KA, et al. *Nat Med.* 2022;28:1381–9.
12. Strauss KA, et al. *Nat Med.* 2022;28:1390–7.
13. DeVivo DC, et al. *Neuromuscul Disord.* 2019;29:842–56.
14. Baranello G, et al. *N Engl J Med.* 2021;384:915–23.
15. Darras BT, et al. *N Engl J Med.* 2021;385:427–35.
16. Darras BT, et al. *Neurology.* 2019;92:e2492–506.
17. Garrison LP, et al. *J Manag Care Spec Pharm.* 2021;27:674–81.
18. Dangouloff T, et al. *Neuromuscul Disord.* 2021;31:574–82.
19. Velikanova R, et al. *Value Health.* 2022;S1098-3015(22)02065-4.
20. Strauss KA, et al. *Nat Med.* 2022;28:1390–7.
21. Mendell JR, et al. *N Engl J Med.* 2017;377:1713–22.
22. Day JD, et al. *Lancet Neurol.* 2021;120:284–93.
23. Mercuri E, et al. *Lancet Neurol.* 2021;20:832–41.
24. De Vivo DC, et al. *Neuromuscul Disord.* 2019;29:842–56.
25. Finkel R, et al. *Neurology.* 2019;92:525-004.
26. Darras BT, et al. *Neurology.* 2019;92:e2492–e2506.
27. Finkel RS, et al. *Neurology.* 2021;96:e281.
28. Darras BT, et al. *N Engl J Med.* 2021;385:427–35.
29. Gregoretti C, et al. *Pediatrics.* 2013;131:e1509–14.
30. Kolb SJ, et al. *Ann Neurol.* 2017;82:883–91.
31. Zerres K, et al. *J Neurol Sci.* 1997;146:67–72.
32. Office of National Statistics. National Life Tables, UK: 2014–2016. Published September 2018. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2014to2016. Accessed September 28, 2022.
33. Wadman RI, et al. *J Neurol.* 2018;25:512–8.
34. Office of National Statistics. Births in England and Wales 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths. Accessed September 28, 2022.
35. Spierzelden Nederland. Richtlijn spinale musculaire atrofie (SMA) type 1. https://www.spierzielden.nl/fileadmin/user_upload/VSN/documenten/Hulpverleners/normalexRichtlijnen/R037-SMA1-Richtlijn-2018.pdf. Accessed September 28, 2022.
36. Sugarman EA, et al. *Eur J Hum Genet.* 2012;20:27–32.
37. Ogino S, et al. *Am J Med Genet.* 2002;110:301–7.
38. Verhaart IEC, et al. Estimates of prevalence of newborn screening for spinal muscular atrophy [Expert Opinion Meeting]. Cisco Webex video conference. 28 September 2020.
39. Alias L, et al. *Hum Genet.* 2009;125:29–39.
40. Vill K, et al. *J Neuromuscul Dis.* 2019;6:503–15.
41. Sun May Arise on SMA: Newborn Screening of Spinal Muscular Atrophy in Belgium. ClinicalTrials.gov identifier: NCT03554343. Updated March 10, 2021. https://clinicaltrials.gov/ct2/show/NCT03554343?cond=NCT03554343&draw=2&rank=1. Accessed September 28, 2022.
42. Ogino S, et al. *Eur J Hum Genet.* 2004;12:1015–23.
43. Heijnen ML, et al. Uitvoeringstoets toevoeging spinale musculaire atrofie aan de neonatale hielprikscreening. [Feasibility study into adding spinal muscular atrophy (SMA) to the newborn blood spot screening] 2020. https://www.rivm.nl/bibliotheek/rapporten/2020-0105.html. Accessed September 28, 2022.
44. NHS. Price List for Rare Disease Services from April 2021. https://www.cuh.nhs.uk/services/referrals/genetics/genetics-laboratories/documents/price-list.pdf. Accessed September 28, 2022.
45. NHS. National Cost Collection for the NHS 2019/2020. https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/. Accessed September 28, 2022.
46. NICE final draft guidance approves life-changing gene therapy for treating spinal muscular atrophy. NICE. 2021. https://www.nice.org.uk/news/article/nice-approves-life-changing-gene-therapy-for-treating-spinal-muscular-atrophy. Accessed September 28, 2022.
47. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/. Accessed September 28, 2022.
48. Thompson R, et al. *Value Health.* 2017;20:2.
49. Tappenden P, et al. Nusinersen for treating spinal muscular atrophy: A single technology appraisal. https://njl-admin.nihr.ac.uk/document/download/2021139. Accessed September 28, 2022.
50. Ara R, et al. *Value Health.* 2010;13:509–18.
51. Wijngaarde CA, et al. *Neurology.* 2020;94:e1634–44.
52. Wijngaarde CA, et al. *Neurology.* 2020;94:e1634–44.

### Abbreviations

ASO, antisense oligonucleotide; DMT, disease-modifying treatment; HCRU, health care resource utilization; HPST, heel-prick screening test; NBS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; *SMN1*, survival motor neuron 1 gene; *SMN2*, survival motor neuron 2 gene.