Cost Effectiveness of Newborn Screening for Spinal Muscular Atrophy in England

EE471

Scan QR code to access the poster

Diana Weidlich[1]; Laurent Servais[2,3]; Imran Kausar[4]; Ruth Howells[5]; Matthias Bischof[6]

[1]Health Economics, Clarivate Analytics, Frankfurt, Germany; [2]MDUK Oxford Neuromuscular Centre, University of Oxford, Oxford, UK; [3]Neuromuscular Center of Liège, Department of Pediatrics, Centre Hospitalier Universitaire de Liège and University of Liège, Liège, Belgium; [4]Novartis Gene Therapies, London, UK; [5]Health Technology Assessment, Clarivate Analytics, Manchester, UK; [6]Novartis Gene Therapies GmbH, Rotkreuz, Switzerland

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]

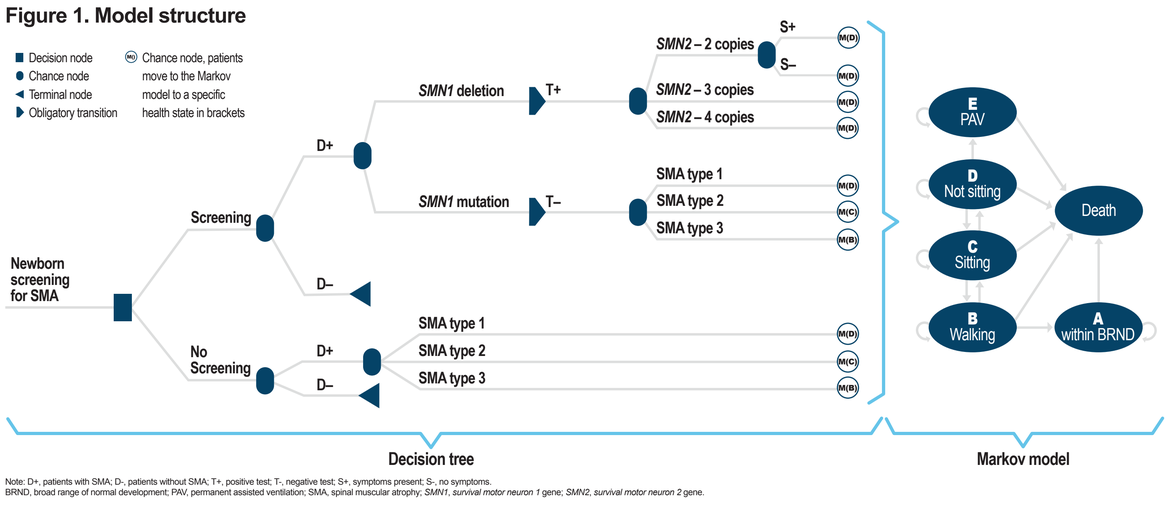
Objective

- 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 are 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.

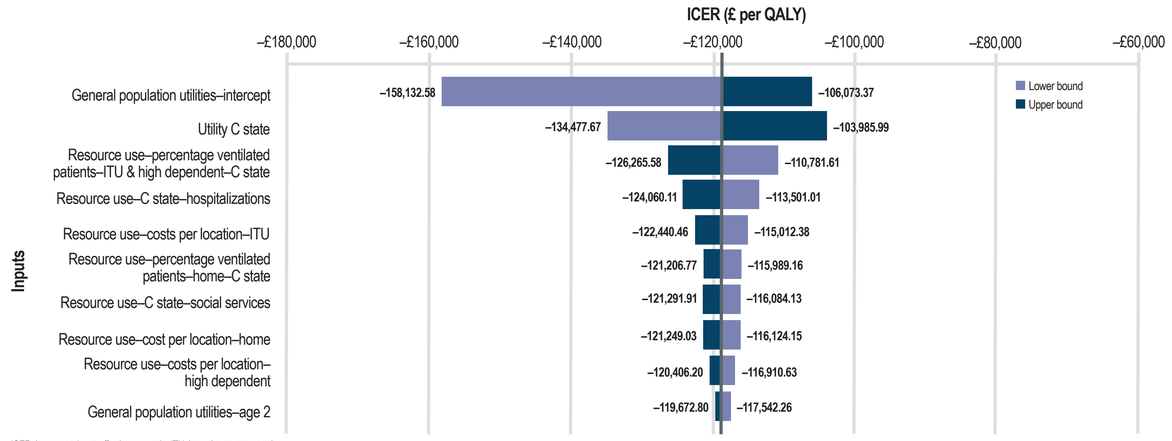
- Base-case results indicated that NBS was dominant (less costly and more effective) compared with non-NBS
- NBS demonstrated a cost saving of £67,238,145 and an estimated gain of 567 QALYs over the lifetime of a newborn cohort identified (approximately 59 patients) per year (**Table 3**)

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

Strategy	Total costs	Total LYs	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 **Figures 3** and **4**) 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 at all willingness-to-pay thresholds relevant to decision-making in England
  - In the probabilistic sensitivity analysis, NBS was associated with mean incremental costs of approximately –£65,366,421 and a mean of 556 QALYs
  - Scenario analyses demonstrated incremental costs of up to approximately –£113 million and gains of approximately 1,071 QALYs
  - **Figure 2. Tornado diagram for the deterministic sensitivity analysis**



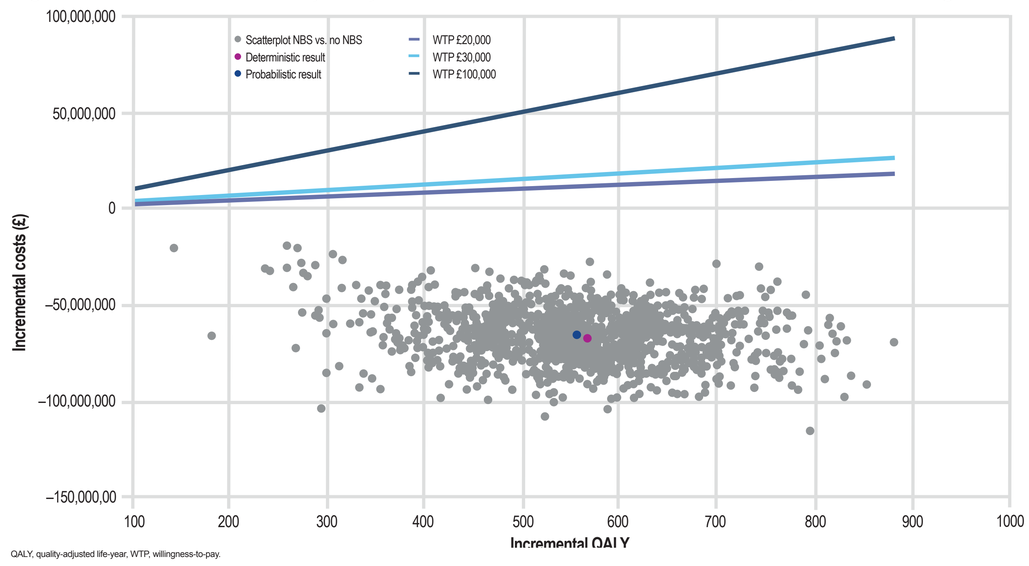
ICER, incremental cost-effectiveness ratio; ITU, intensive treatment unit.

Table 4. Mean probabilistic sensitivity analysis results (discounted)

Strategy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY)	INMB[a]
NBS	£156,598,982	1,160	–£65,366,421	556	Dominant	£84,246,400
Non-NBS	£221,965,402	604				

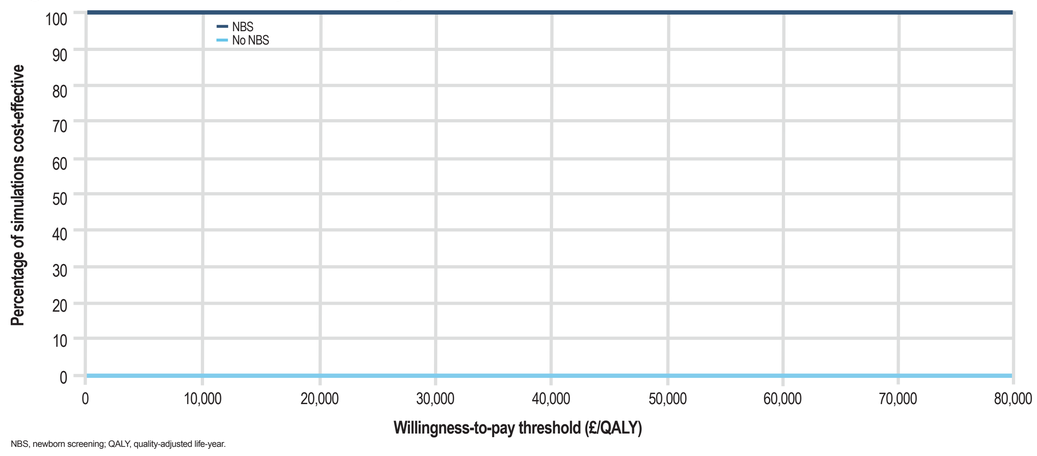
ICER, incremental cost-effectiveness ratio; LY, life-year; NBS, newborn screening; QALY, quality-adjusted life-year.
[a]INMB results are calculated with £30,000/QALY WTP thresholds.

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



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

Figure 4. Cost-effectiveness acceptability curve



NBS, newborn screening; QALY, quality-adjusted life-year.

Table 5. Scenario analysis results

Strategy	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£ per QALY)	INMB[a]
Discount rate of 1.5%								
NBS	£199,020,099	2,329	1,987	–£110,852,776	987	1,071	Dominant	£142,970,467
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	£5,690,074
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	£79,059,471
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	£126,851,360
Non-NBS	£270,993,468	1,151	748					
Societal perspective								
NBS	£161,343,572	1,381	1,177	–£84,146,774	459	567	Dominant	£101,155,028
Non-NBS	£245,490,346	922	610					

ICER, incremental cost-effectiveness ratio; LY, life-year; NBS, newborn screening; QALY, quality-adjusted life-year.
[a]INMB results are calculated with £30,000/QALY WTP thresholds.

Conclusions

- NBS for SMA in England is less costly, with a lifetime savings of £67,238,145 for a newborn cohort identified with SMA per year, 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. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-7228677924741. Accessed October 12, 2022.
21. Strauss KA, et al. *Nat Med.* 2022;28:1390–7.
22. Mendell JR, et al. *N Engl J Med.* 2017;377:1713–22.
23. Day JD, et al. *Lancet Neurol.* 2021;120:284–93.
24. Mercuri E, et al. *Lancet Neurol.* 2021;20:832–41.
25. De Vivo DC, et al. *Neuromuscul Disord.* 2019;29:842–56.
26. Finkel R, et al. *Neurology.* 2019;92:S25.004.
27. Darras BT, et al. *Neurology.* 2019;92:e2492–e2506.
28. Finkel RS, et al. *Neurology.* 2021;96:4281.
29. Darras BT, et al. *N Engl J Med.* 2021;385:427–35.
30. Gregoretti C, et al. *Pediatrics.* 2013;131:e1509–14.
31. Kolb SJ, et al. *Ann Neurol.* 2017;82:883–91.
32. Zarres K, et al. *J Neurol Sci.* 1997;146:67–72.
33. Office of National Statistics. National Life Tables, England 2018–20. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables. Accessed October 12, 2022.
34. Wadman RI, et al. *Eur J Neurol.* 2018;25:512–8.
35. Office of National Statistics. Births in England and Wales 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths. Accessed September 28, 2022.
36. Spierzieken Nederland. Richtlijn. spinale musculaire atrofie (SMA) type 1. https://www.spierziekten.nl/fileadmin/user_upload/VSN/documenten/Huiverenersinformatie/Richtlijnen/R037-SMA1-Richtlijn-2018.pdf. Accessed September 26, 2022.
37. Sugarman EA, et al. *Eur J Hum Genet.* 2012;20:27–32.
38. Ogino S, et al. *Am J Med Genet.* 2002;110:301–7.
39. van der Pol L. Cost-effectiveness of newborn screening for spinal muscular atrophy [Expert Opinion Meeting]. Cisco Webex video conference. 28 September 2020.
40. Alias L, et al. *Hum Genet.* 2009;125:29–39.
41. Vill K, et al. *J Neuromuscul Dis.* 2019;6:503–15.
42. 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.
43. Ogino S, et al. *Eur J Hum Genet.* 2004;12:1015–23.
44. 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.
45. NHS. Price List for Rare Disease Services from April 2021. https://www.ouh.nhs.uk/services/referrals/genetics/genetics-laboratories/documents/price-list.pdf. Accessed September 28, 2022.
46. 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.
47. 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.
48. 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.
49. Thompson R, et al. *Value Health.* 2017;20:2.
50. Tappenden P, et al. Nusinersen for treating spinal muscular atrophy: A single technology appraisal. https://nij-admin.nihr.ac.uk/document/download/2021139. Accessed September 26, 2022.
51. Ara R, et al. *Value Health.* 2010;13:509–18.
52. Wijngaarde CA, et al. *Neurology.* 2020;94:e1634–44.

Abbreviations

ASO, antisense oligonucleotide; DMT, disease-modifying treatment; HCRU, health care resource utilization; NBS, newborn screening; NHS, 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.

Acknowledgments and Disclosures

This study was funded by Novartis Gene Therapies, Inc.

Editorial support was provided by Wynne Dillon, MS, of Kay Square Scientific, Newtown Square, PA. This support was funded by Novartis Gene Therapies, Inc.

Disclosures: DW and **RH** are employees of Clarivate Analytics, which has received consulting fees from Novartis Gene Therapies, Inc., for this research. **IK** and **MB** are employees of Novartis Gene Therapies and own Novartis stock or other equities. **LS** received personal compensation as an advisory committee board member/consultant from Novartis Gene Therapies, Inc., Biogen, Biophytis, Cytokinetics, Dynacure, Roche, Santhera, and Sarepta Therapeutics; and has received research support from NGT, Biogen, Dynacure, and Roche.