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# BMJ Paediatrics Open

## Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective audit

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Keywords:	Respiratory, Neuromuscular, Neurodisability, Costing

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## Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective audit

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## Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen

### Abstract:

Background: Nusinersen has been used to treat spinal muscular atrophy type 1 (SMA1) in the UK since 2017. While initial trials showed neuromuscular benefit from treating SMA1, there is little information on the respiratory effects of nusinersen. We aimed to look at the respiratory care, hospital utilisation and associated costs in newly treated SMA1.

Methods: We reviewed the medical records of all children within the West Midlands with SMA1 treated with nusinersen at Royal Stoke University Hospital. Baseline demographics and hospital admission data were collected including: the reason for admission, total hospital days, HDU days, PICU days, days intubated, discharge diagnosis, doses of nusinersen and treatment complications.

Results: Eleven children (six girls) received nusinersen between May 2017 and April 2019. Their median (range) age was 29 (7–97) months. The median (range) number of nusinersen doses per child was 6 (4-8). All children were receiving long-term ventilatory support; this was non-invasive BiPAP in nine and tracheostomy ventilation in two. The total number of hospital days since diagnosis was 1101 with a median (range) of 118 (7-235) days per child. This included general paediatric ward days 0 (0-63), HDU 79 (7-173) days and PICU 13 (0-109) days per child. This equated to a median (range) of 20 (2 - 72) % of their life in hospital. The estimated cost of this care was £2.2M.

Conclusion: Patients with SMA1 treated with nusinersen spend a considerable proportion of their early life in hospital. Parents should be counselled accordingly. This healthcare utilisation has a significant cost implication.

## Background

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by progressive muscular atrophy and weakness.(1) It has an incidence of 1 in 11,000 live births.(2) There are various subgroups of SMA classified clinically, with SMA type 1 (SMA1) accounting for approximately 60% of cases, and carrying the worst prognosis.(3) Until recently, SMA1 was the commonest genetic disease resulting in death in infancy.(4) Affected children usually present with symptoms before six months of age and historically died from respiratory failure by the age of two years.(5)

SMA1 is caused by the homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene. This results in reduced expression of the SMN protein, which is essential for the survival of motor neurones in the spinal cord and brain stem.(6) Inadequate expression of SMN protein causes degeneration of the motor neurone which in turn causes the associated muscles to atrophy. Humans have a variable number of copies of a second gene, *SMN2* which also encodes for SMN protein.(6) However, *SMN2* is a poor back-up gene and therefore leads to a truncated form of the protein, mostly degraded and a small amount, approximately 10%, of functional full length protein, as a result of aberrant RNA splicing. Approximately 80% of infants with SMA1 have only 1 or 2 copies of *SMN2* and are therefore unable to produce enough functional SMN protein to support normal muscle development.

Nusinersen is an antisense oligonucleotide which works by binding to the *SMN2* mRNA and in order to be effective it must be delivered into the cerebrospinal fluid. This binding modifies splicing of the *SMN2* gene to promote increased production of functional SMN protein.(7) Treatment with nusinersen has the potential to transform prognosis for these children offering hope of treatment for the first time. The drug has been used in the UK since early 2017. The drug costs £450,000 in the first year and £225,000 per annum subsequently and for patients beginning this from before November 2018, the manufacturer provided this free through an Expanded Access Programme.(8) NHSE provides an administration cost, but not the other aspects of care for these patients. While randomised controlled trials showed nusinersen improved motor function and development,(7) it is unclear whether the respiratory consequences produce similar benefits and thus the demands of treatment for families and health economies is yet to be established.

Royal Stoke University Hospital (RSUH) is a regional centre for nusinersen administration and in March 2019 had the second largest cohort of patients in the UK. Before agreeing to act as a regional centre for nusinersen delivery, we carefully considered the potential effects on children, their families and

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2  
3 other healthcare services. However, data were lacking making counselling of families and planning of  
4 service provision difficult. We have carefully monitored healthcare utilisation of SMA1 children  
5 treated with nusinersen. The aim of this article is to report the data on service utilisation for these  
6 children to assist families and healthcare professionals.  
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## 10 **Methods**

11  
12 Patients treated with intrathecal nusinersen at RSUH were identified from a local database. The paper  
13 notes and electronic clinical records were reviewed to collect relevant data from RSUH and the child's  
14 referring hospital. This included baseline demographics, age at diagnosis, details of ventilatory  
15 support, feeding support, number of nusinersen doses, complications following administration and  
16 details of all hospital admissions. Hospital admission data included: duration of admission, number of  
17 HDU days, PICU days and intubated days. Nusinersen usually necessitated admission for one night for  
18 the first dose only.  
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## 26 **Patient and public involvement**

27  
28 No patients were involved in setting the research question or the outcome measures. The results of  
29 this study will be disseminated to patient groups such as SMA UK and MD UK.  
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## 32 **Approval and ethical considerations**

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34 The HRA decision tool (<http://www.hra-decisiontools.org.uk/research>) confirmed this project was  
35 audit not research and so ethical approval was not sought. The audit was approved by the  
36 departmental governance lead.  
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## 41 **Results**

42  
43 We identified eleven children (six girls) who received nusinersen through the Expanded Access  
44 Program at RSUH between May 2017 April 2019. Parents of a 12<sup>th</sup> child declined nusinersen and the  
45 child died at 3 months of age. The median (range) number of nusinersen doses was 6 (4-8). Nine  
46 children received non-invasive BiPAP and two children were ventilated via tracheostomy. Two patients  
47 (including one on tracheostomy ventilation) have died suddenly at home from presumed mucous  
48 plugs, while one other patient had a cardiorespiratory arrest and has suffered hypoxic brain injury.  
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### 54 Duration and location of admissions

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56 In 24 months, the 11 children had spent a total of 1101 days in hospital. The median (range) per child  
57 was 84 (7-235) days. This included a total of 91 general paediatric ward days, 762 HDU days and 248  
58 PICU days. The median (range) per child was 0 (0-63) ward days, 79 (7-173) HDU days and 13 (0-109)  
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PICU days. Three children were responsible for all admissions to the general paediatric ward which occurred at their local hospital. Three children had not been admitted to PICU. Of the eight children that had, six had been intubated for a total of 38 days. The median (range) proportion of life spent in hospital was 20% (2% - 72%). This was very variable with four children spending  $\leq 10\%$ , four 10-35% and three  $>35\%$ .

#### Reason for admission

The median age (range) for initiation of nusinersen was 35 (2 – 372) weeks. Since initiation of nusinersen the eleven children had a total of 107 hospital admissions with a median (range) per child of 11 (1-25). The commonest reason for admission was lower respiratory tract infection (n=42), followed by elective administration of intrathecal nusinersen (n=38). There were seven admissions for gastrointestinal issues, six for an elective sleep study, five for aspiration pneumonia, four for increased secretions or airway issues and three for optimisation of ventilatory support.

#### Trends in admissions

Children in our cohort had the greatest requirement for hospital admission in the first 6 months following nusinersen initiation (see Figure 1). Much of this effect is driven by a tendency for children to have a long first admission (see Figure 2). Subsequent admissions tend to be shorter. The total number of hospital days for the children's first admission was 426 days with a median (range) of 20 (1 -235) days per child.

#### Cost implications and impact on local services

A total of 762 HDU days and 248 PICU days were required by the 11 children in our cohort over two years. This equates to 2.8 days in HDU and 0.93 days in PICU per child each month. RSUH has six HDU (four acute HDU beds and two long term ventilation) and eight PICU beds. The children therefore occupied 17% of the total HDU capacity and 4.2% of the PICU capacity over the study period. Based on current estimates of £1626 per day for a HDU bed and £1785 to £3784 for a PICU bed (depending on the level of care), the additional cost of these HDU/PICU days is £2.2M.(9) This is separate to the cost of the nusinersen and its administration.

Prior to the introduction of nusinersen, patients with SMA1 were generally not admitted for in-patient care, as they were managed within the community and local children's hospices.

## **Discussion**

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3 This is the first study which accurately reports the healthcare utilisation of a cohort of children treated  
4 with nusinersen. This information is vital for those planning healthcare services. In the first two years  
5 after diagnosis, these children spend one fifth of their early life in hospital. This places a significant  
6 burden on parents and families and they should be counselled accordingly. There is a considerable  
7 impact on hospital services, particularly on high dependency and PICU. This involves a substantial extra  
8 resource, in addition to the direct cost of the nusinersen. Reassuringly, the number of hospital days  
9 has reduced as the child gets older.

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12 In addition to the costs associated with in-patient care, these children frequently require care  
13 packages which incur additional community costs. These costs are likely to continue throughout the  
14 child's life. NHSE has decided to fund nusinersen and so the numbers of SMA1 patients surviving and  
15 treated with nusinersen will increase, along with the demand on critical care and community services.  
16 Currently there is no ring-fenced funding for the health needs of SMA1 patients receiving nusinersen  
17 and this is something that must be explored to provide optimal care for these patient without affecting  
18 that of other children requiring critical care services.

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21 We acknowledge the limitations of this study. It includes only eleven patients treated at one centre,  
22 although this is the second largest in the UK. The retrospective nature of the study may have  
23 introduced bias and we did not adjust for potential confounding factors such as socioeconomic status  
24 and co-morbidities. Estimates of the financial burden have concentrated on in-patient rather than  
25 community costs and will therefore be an underestimate.

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28 There is a fall in the number of days spent in hospital. This may be explained by: i) a true improvement  
29 in the respiratory muscle strength of these children over time, or ii) a gradual improvement in the  
30 medical care provided, or iii) an improved ability of these families to cope with their medical conditions  
31 at home and in their own community or iv) deaths within our cohort. Whilst an important  
32 consideration, mortality alone seems unlikely to be the sole driver of this effect as only two children  
33 within the cohort have died at 12 and 16 months respectively.

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36 It may be a function of all of these and we hope that the first three factors will continue to operate.

### 37 38 39 Conclusion

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42 While the improved prognosis and life expectancy associated with nusinersen treatment is exciting  
43 for children with SMA1 and their families, we remain unsure that the respiratory benefits are as great  
44 as that shown for the neurological improvement in the preliminary trials. This study has highlighted  
45 that such children will spend a significant amount of their life in hospital, particularly in the first  
46 months after diagnosis. This places a significant burden on families and on the NHS in general. The



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3 long term outcome for these children is still unknown but the trend for a reduction in hospital days as  
4 the child gets older may be reassuring. Further prospective studies with larger patient numbers are  
5 required to more accurately quantify the health care utilisation by these children and the associated  
6 financial burden.  
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16 What is already known on this topic:

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18 Nusinersen improves prognosis and life expectancy in children with SMA 1.

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20 Infants are now surviving with immense dependency on healthcare services.

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22 NICE has just agreed to fund this new treatment (May 2019).  
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28 What this study adds:

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30 Children with SMA1 who receive Nusinersen have significant ongoing medical costs in addition to the  
31 cost of the drugs received.  
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35 On average this currently is more than £100,000 per patient per year in the first two years of follow  
36 up.  
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39 Associated healthcare costs reduce as time progresses and are less in the second year of life.  
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6 Figure Legend  
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8 Figure 1: Total hospital days per month spent by children following commencement on nusinersen.  
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10 Figure 2: Median length of hospital stay per admission for all children.  
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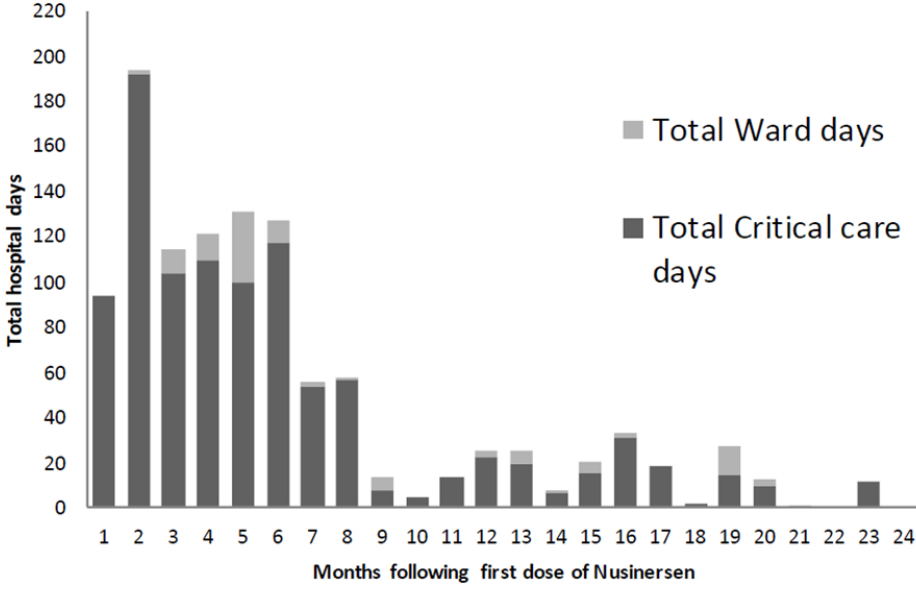
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## Footnotes

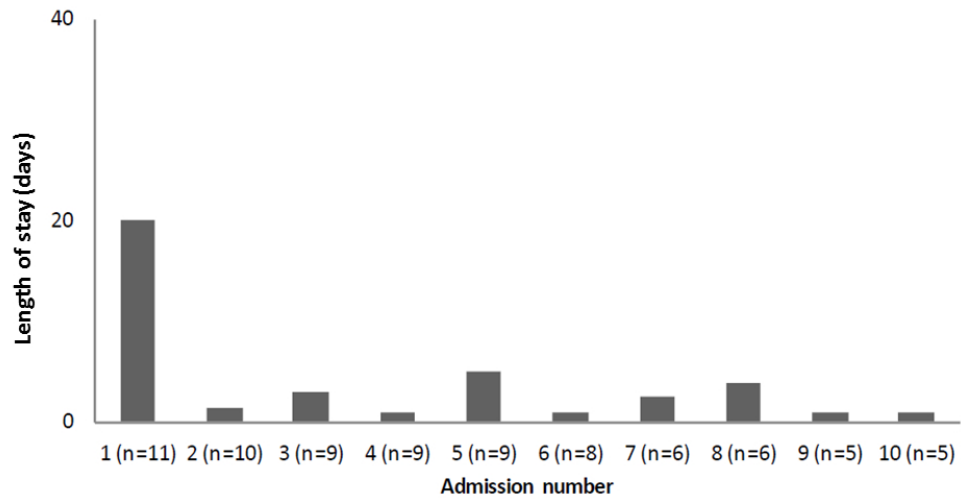
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Transparency: The manuscript's guarantor (MS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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## Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective review

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4 **1 Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen:**  
5 **2 a single centre retrospective review**  
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31  
32 Word Count: 2558 (excluding references)



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3 1 **Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre**  
4 2 **retrospective review**  
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9 4 **Abstract:**

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11 5 **Background:** Nusinersen has been used to treat spinal muscular atrophy type 1 (SMA1) in the UK since  
12 6 2017. While initial trials showed neuromuscular benefit from treating SMA1, there is little information  
13 7 on the respiratory effects of nusinersen. We aimed to look at the respiratory care, hospital utilisation  
14 8 and associated costs in newly treated SMA1.  
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21 10 **Methods:** We reviewed the medical records of all children within the West Midlands with SMA1  
22 11 treated with nusinersen at Royal Stoke University Hospital. Baseline demographics and hospital  
23 12 admission data were collected including: the reason for admission, total hospital days, HDU days, PICU  
24 13 days, days intubated, discharge diagnosis, doses of nusinersen and treatment complications.  
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31 15 **Results:** Eleven children (six girls) received nusinersen between May 2017 and April 2019. Their  
32 16 median (range) age was 29 (7–97) months. The median (range) number of nusinersen doses per child  
33 17 was 6 (4-8). All children were receiving long-term ventilatory support; this was non-invasive BiPAP in  
34 18 nine and tracheostomy ventilation in two. The total number of hospital days since diagnosis was 1101  
35 19 with a median (range) of 118 (7-235) days per child. This included general paediatric ward days 0 (0-  
36 20 63), HDU 79 (7-173) days and PICU 13 (0-109) days per child. This equated to a median (range) of 20  
37 21 (2 - 72) % of their life in hospital. The estimated cost of this care was £2.2M.  
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45  
46 23 **Conclusion:** Patients with SMA1 treated with nusinersen spend a considerable proportion of their  
47 24 early life in hospital. Parents should be counselled accordingly. These data suggest that for every 10  
48 25 children started on nusinersen an extra HDU bed is required. This has a significant cost implication.  
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## 1 Background

2 Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by  
3 progressive muscular atrophy and weakness(1). It has an incidence of 1 in 11,000 live births(2). There  
4 are various subgroups of SMA classified clinically, with SMA type 1 (SMA1) accounting for  
5 approximately 60% of cases, and carrying the worst prognosis(3). Until recently, SMA1 was the  
6 commonest genetic disease resulting in death in infancy(4). Affected children usually present with  
7 symptoms before six months of age and historically died from respiratory failure by the age of two  
8 years(5).

9 SMA1 is caused by the homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene.  
10 This results in reduced expression of the SMN protein, which is essential for the survival of motor  
11 neurones in the spinal cord and brain stem(6). Inadequate expression of SMN protein causes  
12 degeneration of the motor neurone which in turn causes the associated muscles to atrophy. Humans  
13 have a variable number of copies of a second gene, *SMN2* which also encodes for SMN protein(6).  
14 However, *SMN2* transcription in 80-90% of instances leads to production of a truncated, unstable form  
15 of the protein which is non-functional. Approximately 80% of infants with SMA1 have only 1 or 2  
16 copies of *SMN2* and are therefore unable to produce enough functional SMN protein to support  
17 normal muscle development.

18 Nusinersen is an antisense oligonucleotide which works by binding to the *SMN2* mRNA and in order  
19 to be effective it must be delivered into the cerebrospinal fluid. This binding modifies splicing of the  
20 *SMN2* gene to promote increased production of functional SMN protein(7). Treatment with  
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22 the first time. The drug has been used in the UK since early 2017. The drug costs £450,000 in the first  
23 year and £225,000 per annum subsequently. For patients beginning this before November 2018, the  
24 manufacturer provided it free through an Expanded Access Programme(8). NHSE provides an  
25 administration cost, but not the other aspects of care for these patients. While randomised controlled  
26 trials showed nusinersen improved motor function and development(7), it is unclear whether the  
27 respiratory consequences produce similar benefits and thus the demands of treatment for families  
28 and health economies is yet to be established.

29 Royal Stoke University Hospital (RSUH) is the regional centre for nusinersen administration in the West  
30 Midlands which has a population of approximately 6 million. In March 2019 RSUH had the second  
31 largest cohort of SMA1 patients in the UK. Before agreeing to act as a regional centre for nusinersen  
32 delivery, we carefully considered the potential effects on children, their families and other healthcare

1 services. However, data were lacking making counselling of families and planning of service provision  
2 difficult. We have carefully monitored healthcare utilisation of SMA1 children treated with nusinersen.  
3 The aim of this article is to report the data on service utilisation for these children to assist families  
4 and healthcare professionals.

## 5 **Methods**

6 Patients treated with intrathecal nusinersen at RSUH were identified from a local database. The paper  
7 notes and electronic clinical records were reviewed to collect relevant data from RSUH and the child's  
8 referring hospital. This included baseline demographics, age at diagnosis, details of ventilatory  
9 support, feeding support, number of nusinersen doses, complications following administration and  
10 details of all hospital admissions. Hospital admission data included: duration of admission, number of  
11 HDU days, PICU days and intubated days. Nusinersen usually necessitated admission for one night for  
12 the first dose only. All children received care in accordance to the published international guidelines  
13 for the care of children with SMA(9,10). Intrathecal nusinersen was administered by appropriately  
14 trained paediatricians in the PICU treatment room. In babies this was performed using local  
15 anaesthetic and in toddlers using low dose opiate analgesia and / or sedation. No child has required a  
16 general anaesthetic or interventional radiology.

## 17 **Patient and public involvement**

18 No patients were involved in setting the research question or the outcome measures. The results of  
19 this study will be disseminated to patient groups such as SMA UK and MD UK.

## 20 **Approval and ethical considerations**

21 The HRA decision tool (<http://www.hra-decisiontools.org.uk/research>) confirmed this project was  
22 audit not research and so ethical approval was not sought. The audit was approved by the  
23 departmental governance lead.

## 24 **Results**

25 We identified eleven children (six girls) who received nusinersen through the Expanded Access  
26 Program at RSUH between May 2017 and April 2019. Parents of a 12<sup>th</sup> child declined nusinersen and  
27 the child died at 3 months of age. The median (range) number of nusinersen doses was 6 (4-8). Nine  
28 children received non-invasive BiPAP and two children were ventilated via tracheostomy (TIV). Six  
29 children had been commenced on ventilation prior to their first dose of nusinersen. Both patients  
30 receiving TIV had the tracheostomy inserted before nusinersen was commenced. Two patients  
31 (including one on tracheostomy ventilation) have died suddenly at home from presumed mucous

1 plugs at 12 and 16 months of age, while one other patient had a cardiorespiratory arrest and has  
 2 suffered hypoxic brain injury.

3 Table 1: Characteristics of cohort

	Median	Range
Age at diagnosis (months)	16.6	9 – 53.2
Age of first dose nusinersen (months)	20.6	1– 217.2
Age at initiation of LTV 2 (months)	20.9	5.8- 92.5
Age at initiation of advanced care pathway (n= 4) (months)	54	18.1 – 179.4
Number of admissions per child*	11	1 – 25
Number of emergency admissions per child*	3	0 – 21
Number of elective admissions per child*	4	0 – 9
Hospital days per child*	84	7 – 235
General paediatric hospital days per child*	0	0 – 63
HDU days per child*	79	7 – 173
PICU days per child*	13	0 - 109

4 \*Over 24 months.

5 Duration and location of admissions

6 In 24 months, the 11 children had spent a total of 1101 days in hospital. Details of the hospitalisation  
 7 are summarised in Table 1.-Three children were responsible for all admissions to the general paediatric  
 8 ward which occurred at their local hospital. During these admissions, the respiratory team at RSUH  
 9 liaised closely with local providers to guide acute management and arranged transfer when necessary.  
 10 Three children had not been admitted to PICU. Of the eight children that had, six had been intubated  
 11 for a total of 38 days. The median (range) proportion of life spent in hospital was 20% (2% - 72%). This  
 12 was variable with four children spending  $\leq 10\%$ , four 10-35% and three  $>35\%$ .

13 Reason for admission

14 The median age (range) for initiation of nusinersen was 35 (2 – 372) weeks. Since initiation of  
 15 nusinersen the eleven children had a total of 107 hospital admissions with a median (range) per child  
 16 of 11 (1-25). The commonest reason for admission was lower respiratory tract infection (n=42),  
 17 followed by elective administration of intrathecal nusinersen (n=38). There were seven admissions for  
 18 gastrointestinal issues, six for an elective sleep study, five for aspiration pneumonia, four for increased  
 19 secretions or airway issues and three for optimisation of ventilatory support. At each admission for  
 20 nusinersen the patient and family were reviewed by the paediatric palliative care team who

1 administered intrathecal treatment and assessed palliative needs. Children also received  
 2 physiotherapy whilst inpatients. The physiotherapy adjuncts used by patients are listed in table 2. Four  
 3 children had advanced care pathways in place. Between hospital admissions all the children were  
 4 reviewed regularly in the outpatient clinic by the Paediatric Respiratory Multidisciplinary Team.

5 Table 2. Physiotherapy adjuncts that SMA1 children required

Physiotherapy Adjunct	Number (percentage) of children requiring adjunct
Saline Nebulisers	8 (72%)
Suction	11 (100%)
Percussion	9 (82%)
Cough Assist machine	5 (45%)
High Frequency chest wall oscillation vest	1 (0.9%)

### 6 Trends in admissions

7 Children in our cohort had the greatest requirement for hospital admission in the first 6 months  
 8 following nusinersen initiation (see Figure 1). Much of this effect is driven by a tendency for children  
 9 to have a long first admission (see Figure 2). Subsequent admissions tend to be shorter. The total  
 10 number of hospital days for the children's first admission was 426 days with a median (range) of 20 (1  
 11 -235) days per child.

### 12 Cost implications and impact on local services

13 A total of 762 HDU days and 248 PICU days were required by the 11 children in our cohort over two  
 14 years. This equates to 2.8 days in HDU and 0.93 days in PICU per child each month. RSUH has six HDU  
 15 (four acute HDU beds and two long term ventilation) and eight PICU beds. The children therefore  
 16 occupied 17% of the total HDU capacity and 4.2% of the PICU capacity over the study period. Based  
 17 on current estimates of £1626 per day for a HDU bed and £1785 to £3784 for a PICU bed (depending  
 18 on the level of care), the additional cost of these HDU/PICU days is £2.2M(11). This is separate to the  
 19 cost of the nusinersen and its administration.

20 In addition to the costs associated with in-patient care, these children frequently require care  
 21 packages which incur additional community costs. These costs are likely to continue throughout the  
 22 child's life. In this small cohort, we found families highly motivated to provide care for their children  
 23 and no child experienced a prolonged hospital admission as a result of awaiting funding for the  
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3 1 provision of a care package. Four children had care packages implemented: one child had 16 hours  
4 of care a week and three of the children had over 85 hours care per week. These three children  
5 2  
6 3 received care seven nights a week between nine to ten hours and three days a week between five to  
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8 4 eight hours.  
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## 10 5 11 6 12 13 6 14 15 7 **Discussion**

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18 8 This is the first study which accurately reports the in-patient healthcare utilisation of a cohort of  
19 9 children treated with nusinersen. This information is vital for those planning hospital healthcare  
20 10 services. In the first two years after diagnosis, these children spend, on average, one fifth of their early  
21 11 life in hospital although there is considerable inter-individual variation. This places a significant burden  
22 12 on parents and families and they should be counselled accordingly. There is a considerable impact on  
23 13 hospital services, particularly on high dependency and PICU. However, not all children required PICU  
24 14 admission and not all children admitted to PICU required endotracheal intubation. This involves a  
25 15 substantial extra resource, in addition to the direct cost of the nusinersen. Reassuringly, the number  
26 16 of hospital days has reduced as the child grows older. In our cohort, the 11 children required 762 HDU  
27 17 days over 24 months. This equates to the need for an additional HDU bed for every 10 children  
28 18 commenced on nusinersen.

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37 19 NHSE has decided to fund nusinersen for the next five years so the numbers of SMA1 patients surviving  
38 20 and treated with nusinersen will increase, along with the demand on critical care and community  
39 21 services. Currently there is no ring-fenced funding for the health needs of SMA1 patients receiving  
40 22 nusinersen and this is something that must be explored to provide optimal care for these patients  
41 23 without affecting that of other children requiring critical care or general paediatric services. Only a  
42 24 small proportion of admissions was managed wholly at the children's local hospital where expertise  
43 25 in NIV is being slowly developed.

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50 26 We acknowledge the limitations of this study. It includes only eleven patients treated at one centre,  
51 27 although this is the second largest in the UK. The retrospective nature of the study may have  
52 28 introduced bias and we did not adjust for potential confounding factors such as socioeconomic status  
53 29 and co-morbidities. Given the small numbers of children in this cohort we have elected not to report  
54 30 a detailed phenotype and correlation to healthcare utilisation as any observed correlations may be  
55 31 spurious and open to misinterpretation. Instead, we have chosen to consider the cohort as a group as  
56 32 this allows funders, clinicians and those planning healthcare services to make better informed

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3 1 decisions. Estimates of the financial burden have concentrated on in-patient rather than community  
4 costs and will therefore be an underestimate. We could not undertake an accurate review of  
5 2  
6 3 healthcare costs in our region for children with SMA1 prior to the introduction of nusinersen as most  
7 children did not receive active treatment and died in their local hospital. A recent German study  
8 4  
9 5 estimated the total direct cost of illness for children with SMA1 to be €99,664 per year(12).

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12 6 As the children grow older, there is a fall in the number of days spent in hospital. This is in part due to  
13 a prolonged first admission, during which the child was stabilised and the family were trained and  
14 7  
15 8 counselled. It may also be explained by: i) a true improvement in the respiratory muscle strength of  
16 9  
17 10 these children over time, or ii) a gradual improvement in the medical care provided, or iii) an improved  
18 ability of these families to cope with their medical conditions at home and in their own community or  
19 11  
20 12 iv) deaths within our cohort. Whilst an important consideration, mortality alone seems unlikely to be  
21 the sole driver of this effect as only two children within the cohort have died. It may be a function of  
22 13  
23 14 all of these and we hope that the first three factors will continue to operate.

#### 24 25 26 14 Conclusion

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29 15 While the improved prognosis and life expectancy associated with nusinersen treatment is exciting  
30 16  
31 17 for children with SMA1 and their families, we remain unsure that the respiratory benefits are as great  
32 as that shown for the neurological improvement in the preliminary trials. This study has highlighted  
33 18  
34 19 that such children will spend a significant amount of their life in hospital, particularly in the first  
35 months after diagnosis. This places a significant burden on families and on the NHS in general. The  
36 20  
37 21 long term outcome for these children is still unknown but the trend for a reduction in hospital days as  
38 the child grows older may be reassuring. Further prospective studies with larger patient numbers are  
39 22  
40 23 required to more accurately quantify the longer term health care utilisation by these children and the  
41 associated financial burden.  
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What is already known on this topic:

Nusinersen improves prognosis and life expectancy in children with SMA 1.

Infants are now surviving with immense dependency on healthcare services.

NICE agreed in May 2019 to fund this new treatment.

What this study adds:

Children with SMA1 who receive Nusinersen have significant ongoing medical costs in addition to the cost of the drugs received.

On average this currently is more than £100,000 per patient per year in the first two years of follow up.

Associated healthcare costs reduce as time progresses and are less in the second year of life.

Confidential: For Review Only



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1 Figure Legend

2 Figure 1: Total hospital days per month spent by children following commencement on nusinersen.

3 Figure 2: Median length of hospital stay per admission for all children.

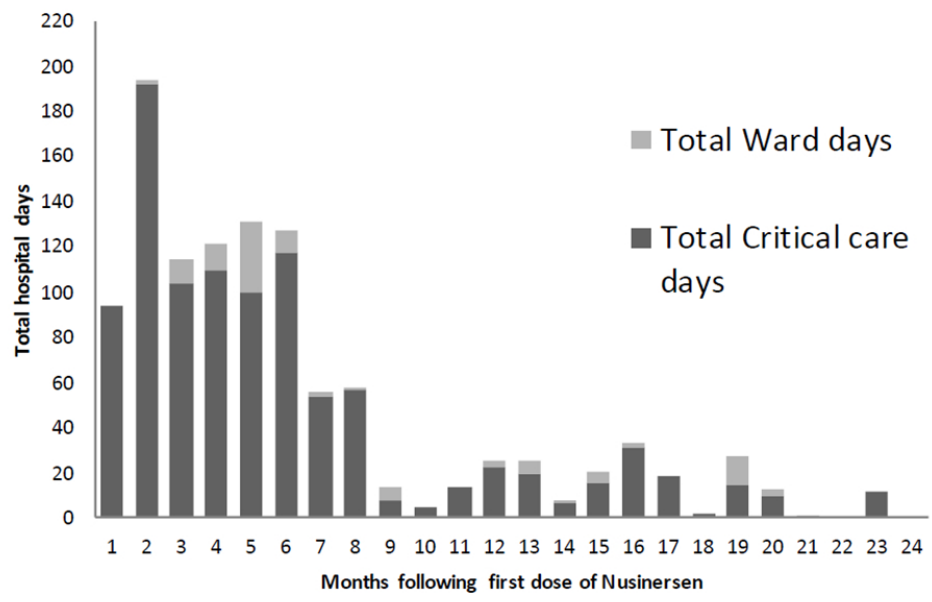
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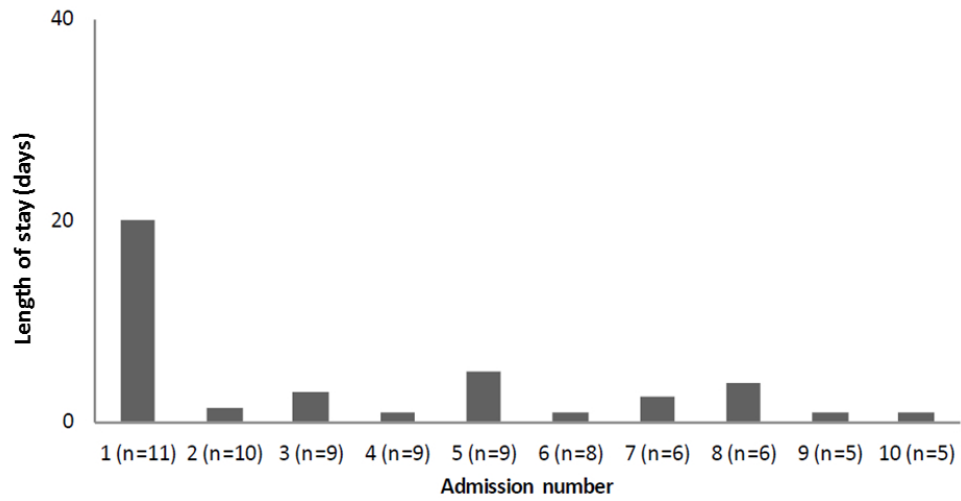
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6 2 Contributors: MS and JA originated the design of the study. IA collected the data and drafted the  
7  
8 3 manuscript. FG and MS supervised the writing. IA, FG, WC, MS, JA, SC, TW and RK revised each draft  
9  
10 4 for important intellectual content. All authors read and approved the final manuscript. MS had  
11  
12 5 primary responsibility for the final content and is the guarantor. The corresponding author (MS)  
13  
14 6 attests that all listed authors meet authorship criteria and that no others meeting the criteria have  
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16 7 been omitted.

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18 8 Transparency: The manuscript's guarantor (MS) affirms that the manuscript is an honest, accurate,  
19  
20 9 and transparent account of the study being reported; that no important aspects of the study have  
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22 10 been omitted; and that any discrepancies from the study as planned have been explained.  
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# BMJ Paediatrics Open

## Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective review

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Keywords:	Respiratory, Neuromuscular, Neurodisability, Costing

SCHOLARONE™  
Manuscripts

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3 **1 Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen:**  
4 **a single centre retrospective review**  
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57 32 Word Count: 2558 (excluding references)

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3 1 **Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre**  
4 2 **retrospective review**  
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9 4 **Abstract:**

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11 5 Background: Nusinersen has been used to treat spinal muscular atrophy type 1 (SMA1) in the UK since  
12 6 2017. While initial trials showed neuromuscular benefit from treating SMA1, there is little information  
13 7 on the respiratory effects of nusinersen. We aimed to look at the respiratory care, hospital utilisation  
14 8 and associated costs in newly treated SMA1.  
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21 10 Methods: We reviewed the medical records of all children within the West Midlands with SMA1  
22 11 treated with nusinersen at Royal Stoke University Hospital. Baseline demographics and hospital  
23 12 admission data were collected including: the reason for admission, total hospital days, HDU days, PICU  
24 13 days, days intubated, discharge diagnosis, doses of nusinersen and treatment complications.  
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31 15 Results: Eleven children (six girls) received nusinersen between May 2017 and April 2019. Their  
32 16 median (range) age was 29 (7–97) months. The median (range) number of nusinersen doses per child  
33 17 was 6 (4-8). All children were receiving long-term ventilatory support; this was non-invasive BiPAP in  
34 18 nine and tracheostomy ventilation in two. The total number of hospital days since diagnosis was 1101  
35 19 with a median (range) of 118 (7-235) days per child. This included general paediatric ward days 0 (0-  
36 20 63), HDU 79 (7-173) days and PICU 13 (0-109) days per child. This equated to a median (range) of 20  
37 21 (2 - 72) % of their life in hospital. The estimated cost of this care was £2.2M.  
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46 23 Conclusion: Patients with SMA1 treated with nusinersen spend a considerable proportion of their  
47 24 early life in hospital. Parents should be counselled accordingly. These data suggest that for every 10  
48 25 children started on nusinersen an extra HDU bed is required. This has a significant cost implication.  
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## 1 Background

2 Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by  
3 progressive muscular atrophy and weakness(1). It has an incidence of 1 in 11,000 live births(2). There  
4 are various subgroups of SMA classified clinically, with SMA type 1 (SMA1) accounting for  
5 approximately 60% of cases, and carrying the worst prognosis(3). Until recently, SMA1 was the  
6 commonest genetic disease resulting in death in infancy(4). Affected children usually present with  
7 symptoms before six months of age and historically died from respiratory failure by the age of two  
8 years(5).

9 SMA1 is caused by the homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene.  
10 This results in reduced expression of the SMN protein, which is essential for the survival of motor  
11 neurones in the spinal cord and brain stem(6). Inadequate expression of SMN protein causes  
12 degeneration of the motor neurone which in turn causes the associated muscles to atrophy. Humans  
13 have a variable number of copies of a second gene, *SMN2* which also encodes for SMN protein(6).  
14 However, *SMN2* transcription in 80-90% of instances leads to production of a truncated, unstable form  
15 of the protein which is non-functional. Approximately 80% of infants with SMA1 have only 1 or 2  
16 copies of *SMN2* and are therefore unable to produce enough functional SMN protein to support  
17 normal muscle development.

18 Nusinersen is an antisense oligonucleotide which works by binding to the *SMN2* mRNA and in order  
19 to be effective it must be delivered into the cerebrospinal fluid. This binding modifies splicing of the  
20 *SMN2* gene to promote increased production of functional SMN protein(7). Treatment with  
21 nusinersen has the potential to transform prognosis for these children offering hope of treatment for  
22 the first time. The drug has been used in the UK since early 2017. The drug costs £450,000 in the first  
23 year and £225,000 per annum subsequently. For patients beginning this before November 2018, the  
24 manufacturer provided it free through an Expanded Access Programme(8). NHSE provides an  
25 administration cost, but not the other aspects of care for these patients. While randomised controlled  
26 trials showed nusinersen improved motor function and development(7), it is unclear whether the  
27 respiratory consequences produce similar benefits and thus the demands of treatment for families  
28 and health economies is yet to be established.

29 Royal Stoke University Hospital (RSUH) is the regional centre for nusinersen administration in the West  
30 Midlands which has a population of approximately 6 million. In March 2019 RSUH had the second  
31 largest cohort of SMA1 patients in the UK. Before agreeing to act as a regional centre for nusinersen  
32 delivery, we carefully considered the potential effects on children, their families and other healthcare

1 services. However, data were lacking making counselling of families and planning of service provision  
2 difficult. We have carefully monitored healthcare utilisation of SMA1 children treated with nusinersen.  
3 The aim of this article is to report the data on service utilisation for these children to assist families  
4 and healthcare professionals.

## 5 **Methods**

6 Patients treated with intrathecal nusinersen at RSUH were identified from a local database. The paper  
7 notes and electronic clinical records were reviewed to collect relevant data from RSUH and the child's  
8 referring hospital. This included baseline demographics, age at diagnosis, details of ventilatory  
9 support, feeding support, number of nusinersen doses, complications following administration and  
10 details of all hospital admissions. Hospital admission data included: duration of admission, number of  
11 HDU days, PICU days and intubated days. Nusinersen usually necessitated admission for one night for  
12 the first dose only. All children received care in accordance to the published international guidelines  
13 for the care of children with SMA(9,10). Intrathecal nusinersen was administered by appropriately  
14 trained paediatricians in the PICU treatment room. In babies this was performed using local  
15 anaesthetic and in toddlers using low dose opiate analgesia and / or sedation. No child has required a  
16 general anaesthetic or interventional radiology.

## 17 **Patient and public involvement**

18 No patients were involved in setting the research question or the outcome measures. The results of  
19 this study will be disseminated to patient groups such as SMA UK and MD UK.

## 20 **Approval and ethical considerations**

21 The HRA decision tool (<http://www.hra-decisiontools.org.uk/research>) confirmed this project was  
22 audit not research and so ethical approval was not sought. The audit was approved by the  
23 departmental governance lead.

## 24 **Results**

25 We identified eleven children (six girls) who received nusinersen through the Expanded Access  
26 Program at RSUH between May 2017 and April 2019. Parents of a 12<sup>th</sup> child declined nusinersen and  
27 the child died at 3 months of age. The median (range) number of nusinersen doses was 6 (4-8). Nine  
28 children received non-invasive BiPAP and two children were ventilated via tracheostomy (TIV). Six  
29 children had been commenced on ventilation prior to their first dose of nusinersen. Both patients  
30 receiving TIV had the tracheostomy inserted before nusinersen was commenced. Two patients  
31 (including one on tracheostomy ventilation) have died suddenly at home from presumed mucous

1 plugs at 12 and 16 months of age, while one other patient had a cardiorespiratory arrest and has  
 2 suffered hypoxic brain injury.

3 Table 1: Characteristics of cohort

	Median	Range
Age at diagnosis (months)	16.6	9 – 53.2
Age of first dose nusinersen (months)	20.6	1– 217.2
Age at initiation of LTV 2 (months)	20.9	5.8- 92.5
Age at initiation of advanced care pathway (n= 4) (months)	54	18.1 – 179.4
Number of admissions per child*	11	1 – 25
Number of emergency admissions per child*	3	0 – 21
Number of elective admissions per child*	4	0 – 9
Hospital days per child*	84	7 – 235
General paediatric hospital days per child*	0	0 – 63
HDU days per child*	79	7 – 173
PICU days per child*	13	0 - 109

4 \*Over 24 months.

5 Duration and location of admissions

6 In 24 months, the 11 children had spent a total of 1101 days in hospital. Details of the hospitalisation  
 7 are summarised in Table 1.-Three children were responsible for all admissions to the general paediatric  
 8 ward which occurred at their local hospital. During these admissions, the respiratory team at RSUH  
 9 liaised closely with local providers to guide acute management and arranged transfer when necessary.  
 10 Three children had not been admitted to PICU. Of the eight children that had, six had been intubated  
 11 for a total of 38 days. The median (range) proportion of life spent in hospital was 20% (2% - 72%). This  
 12 was variable with four children spending  $\leq 10\%$ , four 10-35% and three  $>35\%$ .

13 Reason for admission

14 The median age (range) for initiation of nusinersen was 35 (2 – 372) weeks. Since initiation of  
 15 nusinersen the eleven children had a total of 107 hospital admissions with a median (range) per child  
 16 of 11 (1-25). The commonest reason for admission was lower respiratory tract infection (n=42),  
 17 followed by elective administration of intrathecal nusinersen (n=38). There were seven admissions for  
 18 gastrointestinal issues, six for an elective sleep study, five for aspiration pneumonia, four for increased  
 19 secretions or airway issues and three for optimisation of ventilatory support. At each admission for  
 20 nusinersen the patient and family were reviewed by the paediatric palliative care team who

administered intrathecal treatment and assessed palliative needs. Children also received physiotherapy whilst inpatients. The physiotherapy adjuncts used by patients are listed in table 2. Four children had advanced care pathways in place. Between hospital admissions all the children were reviewed regularly in the outpatient clinic by the Paediatric Respiratory Multidisciplinary Team.

Table 2. Physiotherapy adjuncts that SMA1 children required

Physiotherapy Adjunct	Number (percentage) of children requiring adjunct
Saline Nebulisers	8 (72%)
Suction	11 (100%)
Percussion	9 (82%)
Cough Assist machine	5 (45%)
High Frequency chest wall oscillation vest	1 (0.9%)

### Trends in admissions

Children in our cohort had the greatest requirement for hospital admission in the first 6 months following nusinersen initiation (see Figure 1). Much of this effect is driven by a tendency for children to have a long first admission (see Figure 2). Subsequent admissions tend to be shorter. The total number of hospital days for the children's first admission was 426 days with a median (range) of 20 (1-235) days per child.

### Cost implications and impact on local services

A total of 762 HDU days and 248 PICU days were required by the 11 children in our cohort over two years. This equates to 2.8 days in HDU and 0.93 days in PICU per child each month. RSUH has six HDU (four acute HDU beds and two long term ventilation) and eight PICU beds. The children therefore occupied 17% of the total HDU capacity and 4.2% of the PICU capacity over the study period. Based on current estimates of £1626 per day for a HDU bed and £1785 to £3784 for a PICU bed (depending on the level of care), the additional cost of these HDU/PICU days is £2.2M(11). This is separate to the cost of the nusinersen and its administration.

In addition to the costs associated with in-patient care, these children frequently require care packages which incur additional community costs. These costs are likely to continue throughout the child's life. In this small cohort, we found families highly motivated to provide care for their children and no child experienced a prolonged hospital admission as a result of awaiting funding for the provision of a care package. Four children had care packages implemented: one child had 16 hours

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3 1 of care a week and three of the children had over 85 hours care per week. These three children  
4 2 received care seven nights a week between nine to ten hours and three days a week between five to  
5 3 eight hours. One with a large care package had tracheostomy ventilation, but the parents of the  
6 4 other child with tracheostomy declined a care package.  
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## 6 **Discussion**

7 This is the first study which accurately reports the in-patient healthcare utilisation of a cohort of  
8 children treated with nusinersen. This information is vital for those planning hospital healthcare  
9 services. In the first two years after diagnosis, these children spend, on average, one fifth of their early  
10 life in hospital although there is considerable inter-individual variation. This places a significant burden  
11 on parents and families and they should be counselled accordingly. There is a considerable impact on  
12 hospital services, particularly on high dependency and PICU. However, not all children required PICU  
13 admission and not all children admitted to PICU required endotracheal intubation. This involves a  
14 substantial extra resource, in addition to the direct cost of the nusinersen. Reassuringly, the number  
15 of hospital days has reduced as the child grows older. In our cohort, the 11 children required 762 HDU  
16 days over 24 months. This equates to the need for an additional HDU bed for every 10 children  
17 commenced on nusinersen.

18 NHSE has decided to fund nusinersen for the next five years so the numbers of SMA1 patients surviving  
19 and treated with nusinersen will increase, along with the demand on critical care and community  
20 services. Currently there is no ring-fenced funding for the health needs of SMA1 patients receiving  
21 nusinersen and this is something that must be explored to provide optimal care for these patients  
22 without affecting that of other children requiring critical care or general paediatric services. Only a  
23 small proportion of admissions was managed wholly at the children's local hospital where expertise  
24 in NIV is being slowly developed.

25 We acknowledge the limitations of this study. It includes only eleven patients treated at one centre,  
26 although this is the second largest in the UK. The retrospective nature of the study may have  
27 introduced bias and we did not adjust for potential confounding factors such as socioeconomic status  
28 and co-morbidities. Given the small numbers of children in this cohort we have elected not to report  
29 a detailed phenotype and correlation to healthcare utilisation as any observed correlations may be  
30 spurious and open to misinterpretation. Instead, we have chosen to consider the cohort as a group as  
31 this allows funders, clinicians and those planning healthcare services to make better informed  
32 decisions. Estimates of the financial burden have concentrated on in-patient rather than community  
33 costs and will therefore be an underestimate. We could not undertake an accurate review of

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3 1 healthcare costs in our region for children with SMA1 prior to the introduction of nusinersen as most  
4 2 children did not receive active treatment and died in their local hospital. A recent German study  
5 3 estimated the total direct cost of illness for children with SMA1 to be €99,664 per year<sup>(12)</sup>.  
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9 4 As the children grow older, there is a fall in the number of days spent in hospital. This is in part due to  
10 5 a prolonged first admission, during which the child was stabilised and the family were trained and  
11 6 counselled. It may also be explained by: i) a true improvement in the respiratory muscle strength of  
12 7 these children over time, or ii) a gradual improvement in the medical care provided, or iii) an improved  
13 8 ability of these families to cope with their medical conditions at home and in their own community or  
14 9 iv) deaths within our cohort. Whilst an important consideration, mortality alone seems unlikely to be  
15 10 the sole driver of this effect as only two children within the cohort have died. It may be a function of  
16 11 all of these and we hope that the first three factors will continue to operate.  
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## 22 Conclusion

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25 13 While the improved prognosis and life expectancy associated with nusinersen treatment is exciting  
26 14 for children with SMA1 and their families, we remain unsure that the respiratory benefits are as great  
27 15 as that shown for the neurological improvement in the preliminary trials. This study has highlighted  
28 16 that such children will spend a significant amount of their life in hospital, particularly in the first  
29 17 months after diagnosis. This places a significant burden on families and on the NHS in general. The  
30 18 long term outcome for these children is still unknown but the trend for a reduction in hospital days as  
31 19 the child grows older may be reassuring. Further prospective studies with larger patient numbers are  
32 20 required to more accurately quantify the longer term health care utilisation by these children and the  
33 21 associated financial burden.  
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1 What is already known on this topic:

2 Nusinersen improves prognosis and life expectancy in children with SMA 1.

3 Infants are now surviving with immense dependency on healthcare services.

4 NICE agreed in May 2019 to fund this new treatment.

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6 What this study adds:

7 Children with SMA1 who receive Nusinersen have significant ongoing medical costs in addition to the  
8 cost of the drugs received.

9 On average this currently is more than £100,000 per patient per year in the first two years of follow  
10 up.

11 Associated healthcare costs reduce as time progresses and are less in the second year of life.

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1 Figure 1: Total hospital days per month spent by children following commencement on nusinersen.

2 Figure 2: Median length of hospital stay per admission for all children.

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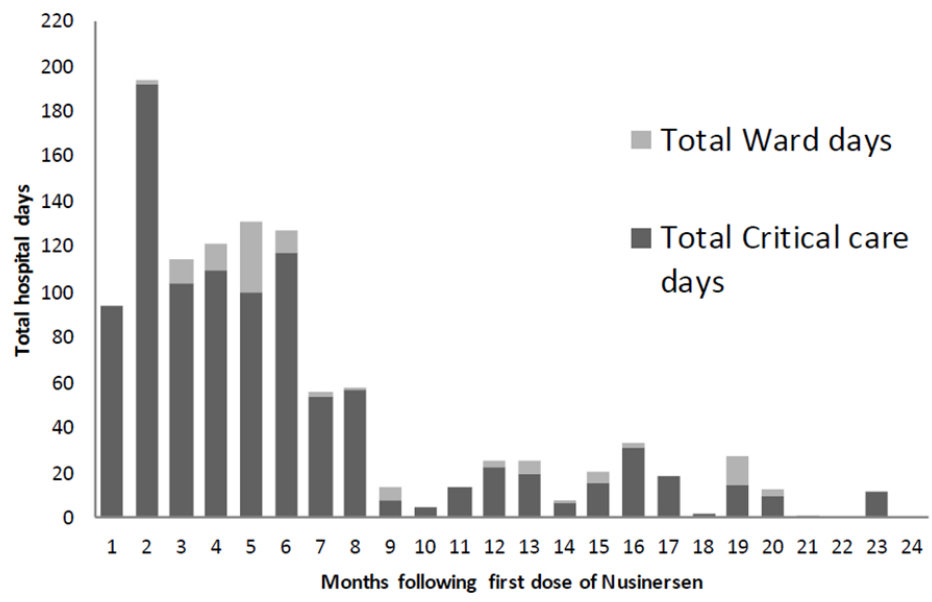
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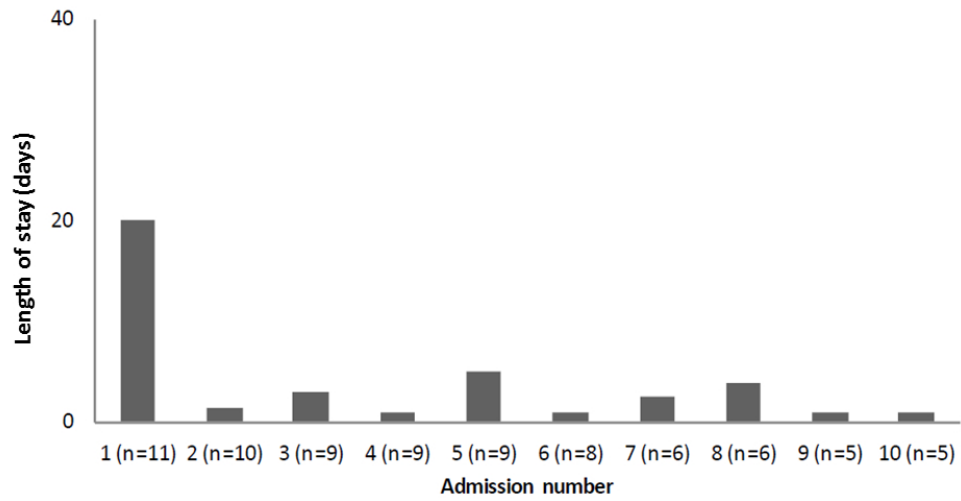
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3 1 Contributors: MS and JA originated the design of the study. IA collected the data and drafted the  
4 manuscript. FG and MS supervised the writing. IA, FG, WC, MS, JA, SC, TW and RK revised each draft  
5 2  
6 3 for important intellectual content. All authors read and approved the final manuscript. MS had  
7 4  
8 5 primary responsibility for the final content and is the guarantor. The corresponding author (MS)  
9 6  
10 7 attests that all listed authors meet authorship criteria and that no others meeting the criteria have  
11 8  
12 9 been omitted.

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14 7 Transparency: The manuscript's guarantor (MS) affirms that the manuscript is an honest, accurate,  
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16 9 and transparent account of the study being reported; that no important aspects of the study have  
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18 been omitted; and that any discrepancies from the study as planned have been explained.  
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