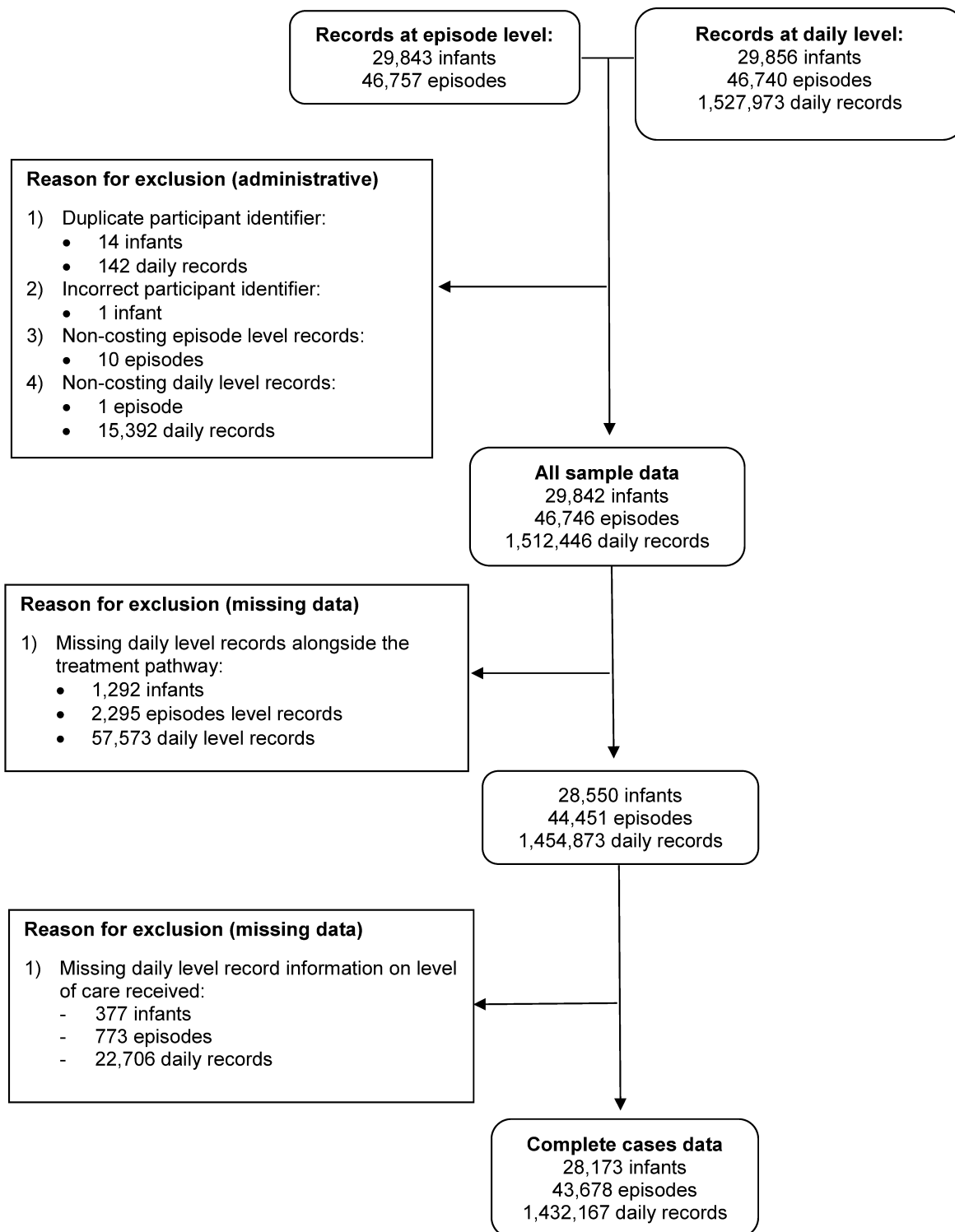


## Supplementary file

### Multiple Imputation Methods

An imputation model was constructed, that included complete data on baseline baby and maternal characteristics, and the total cost of care provided at each level of care (intensive care, high-dependency care, special care without carer, special care with carer and normal care). We imputed costs for each level of care for babies with missing data (see Figure A1 below). Baseline characteristics included gestational age at birth, gender, number of fetuses, birthweight, neonatal death, maternal age and mode of delivery. All baseline covariates were subject to a small number of missing data that was imputed using conditional mean imputation prior to inclusion in the imputation model. A predictive mean matching estimation using chained equations with 50 imputations was implemented [1]. Mean estimates and estimates of standard errors were combined between imputed datasets using Rubin's rule [2] without any adjustment. Combined mean cost estimates and adjusted standard errors (SE) by gestational week across imputed datasets are shown to report the results of the multiple imputation analysis (Table A5 below).

**Figure A1: Flow of NNRD data available to estimate neonatal care costs for the very preterm babies discharged from neonatal units in England between 2014-2018.**



**Table A1: Unit costs (expressed in 2018/19 UK pound sterling) used within the cost analysis**

Resource Use Item	Unit cost 2018/19 UK £	Source
<i>Neonatal unit inpatient bed days</i>		
- intensive care level	£1,531	National Cost Collection Data Publication. National Schedule of NHS Costs 2018/19. HRG code XA01Z [3]
- high dependency care level	£1,007	National Cost Collection Data Publication. National Schedule of NHS Costs 2018/19. HRG code XA02Z [3]
- special care level, (carer not resident alongside baby)	£661	National Cost Collection Data Publication. National Schedule of NHS Costs 2018/19. HRG code XA03Z [3]
- special care level, (carer resident at cot-side and caring for baby)	£493	National Cost Collection Data Publication. National Schedule of NHS Costs 2018/19. HRG code XA04Z [3]
- normal care level	£514	National Cost Collection Data Publication. National Schedule of NHS Costs 2018/19. HRG code XA05Z [3]
Neonatal Critical Care, Transportation	£1,257	National Cost Collection Data Publication. National Schedule of NHS Costs 2018/19. HRG code XA06Z [3]
Inhaled nitric oxide (iNO) (per day)	£267	European iNO Registry for Liverpool Women's NHS Foundation Trust
<i>Surfactant replacement – poractant alfa (per day, by birth weight)*</i>		
- Birth weight ≤0.6kg (1 bottle 1.5ml)	£282	British National Formulary online: NHS indicative price [4]
- 0.7kg ≤ Birth weight ≤1.2kg (1 bottle 3ml)	£547	
- 1.3kg ≤ Birth weight ≤1.8kg (1 bottle 3ml and 1 bottle 1.5ml)	£829	
- 1.9kg ≤ Birth weight ≤2.4kg (2 bottles 3ml)	£1,095	
- 2.5kg ≤ Birth weight ≤3kg (2 bottles 3ml and 1 bottle 1.5ml)	£1,376	
- 3.1kg ≤ Birth weight ≤3.6kg (3 bottles 3ml)	£1,642	
- 3.7kg ≤ Birth weight ≤4.2kg (3 bottles 3ml and 1 bottle 1.5ml)	£1,924	
Total parental nutrition (per day, over 14 days of use)**	£48	Walter et al. (2012); inflated to 2018/19 prices [5]
Palivizumab (per day at 15ml/kg birth weight)	£435	British National Formulary online: NHS indicative price [4]
ROP surgery	£1,731	National Cost Collection Data Publication. National Schedule of NHS Costs 2018/19. HRG code BZ86C, elective care [3]
Neonatal surgery***	Various	HRG4+ 2017/18 Reference Costs Grouper; inflated to 2018/19 prices [6]

ROP: retinopathy of prematurity;

\*Surfactant use was reported from 3 separate fields from the datasets: Surfactant given today, Drugs given today and Surfactant given at resuscitation. The first two variables were recorded at the daily level, while the third variable was recorded at the episode level and therefore we defined its use for the first daily record of this episode;

\*\*The use of total parental nutrition (TPN) was reported from 2 separate fields from the datasets: TPN given today and Drugs given today;

\*\*\*Different types of neonatal surgery were identified from OPCS and ICD-10 codes using the HRG4+ 2017/18 Reference Costs Grouper Software.

**Table A2: Baseline characteristics of babies born between 27 and 31 weeks gestation with and without missing NNRD data on daily records or level of daily care provided – data are frequencies (percentages) unless otherwise stated**

	Babies with missing daily records or level of care data (n=1,669)	Babies with complete information (n=28,173)	p value*
	n (%)	n (%)	
<b>Gestational age at birth</b>			
27 weeks	284 (17.0%)	3,296 (11.7%)	p<0.001
28 weeks	304 (18.2%)	4,370 (15.5%)	
29 weeks	289 (17.3%)	5,036 (17.9%)	
30 weeks	354 (21.2%)	6,625 (23.5%)	
31 weeks	435 (26.1%)	8,827 (31.3%)	
Missing	3 (0.2%)	19 (0.1%)	
<b>Gender of baby</b>			
Male	961 (57.6%)	15,363 (54.5%)	0.046
Female	704 (42.2%)	12,755 (45.3%)	
Missing	4 (0.2%)	55 (0.2%)	
<b>Number of fetus</b>			
Singleton birth	1,229 (73.6%)	20,555 (73.0%)	0.632
Multiple birth	438 (26.2%)	7,598 (27.0%)	
Missing	2 (0.1%)	20 (0.1%)	
<b>Birthweight (g) - mean(SD)</b>	1,282.6 (358.2)	1,330.2 (332.2)	p<0.001
Missing	8 (0.5%)	82 (0.3%)	
<b>Apgar score at 5min - mean(SD)</b>	8.1 (1.7)	8.1 (1.8)	0.030
Missing	156 (9.4%)	2,877 (10.2%)	
<b>Died in neonatal care</b>	22 (1.3%)	985 (3.5%)	p<0.001
Missing	1 (0.1%)	0 (0.0%)	

SD: standard deviation; \*Continuous variables were tested by independent t-test, categorical variables by chi-square test

**Table A3: A comparison of gestational age at birth between very preterm births in the study cohort and those identified from national live births statistics for England for in 2016, 2017 and 2018**

Year	Study cohort	National data for England from Office for National Statistics (ONS)	p-value*
<b>2016</b>			
27	704 (12.6%)	768 (12.6%)	
28	883 (15.8%)	950 (15.5%)	
29	1,015 (18.2%)	1,101 (18.0%)	0.977
30	1,282 (23.0%)	1,412 (23.1%)	
31	1,689 (30.3%)	1,881 (30.8%)	
<b>2017</b>			
27	638 (11.7%)	690 (11.6%)	
28	860 (15.7%)	949 (16.0%)	
29	991 (18.1%)	1,078 (18.2%)	0.987
30	1,305 (23.9%)	1,427 (24.1%)	
31	1,670 (30.6%)	1,787 (30.1%)	
<b>2018</b>			
27	476 (11.0%)	696 (12.0%)	
28	620 (14.3%)	888 (15.3%)	
29	760 (17.5%)	1,039 (17.9%)	0.151
30	1,035 (23.8%)	1,358 (23.4%)	
31	1,448 (33.3%)	1,835 (31.6%)	

\*chi-square test of proportions

Source: Office for National Statistics; births extracted from a dataset containing birth registrations. 2016 and 2017 figures exclude births where mothers' usual residence was outside of England. 2018 figures include births where mothers' usual residence was in England and Wales. All figures were based on babies born in the calendar year.

**Table A4: Counts of hospital transfers, surgeries and days receiving other non-routine procedures during neonatal admissions for very preterm babies in England for the period 2014-2018 (n = 28,154)\***

	<b>27 weeks gestation n=3,296</b>	<b>28 weeks gestation n=4,370</b>	<b>29 weeks gestation n=5,036</b>	<b>30 weeks gestation n=6,625</b>	<b>31 weeks gestation n=8,827</b>
<b>Hospital transfer within 24 hours of birth</b>					
Number of transfers	287	330	293	286	311
Number (%) of babies receiving	276 (8.4%)	323 (7.4%)	286 (5.7%)	282 (4.3%)	307 (3.5%)
<b>Hospital transfer after 24 hours of birth</b>					
Number of transfers	872	836	713	659	571
Number (%) of babies receiving	654 (19.8%)	665 (15.2%)	593 (11.8%)	588 (8.9%)	523 (5.9%)
<b>Nitric oxide</b>					
Number of days of care	1,333	1,363	953	918	660
Number (%) of babies receiving	425 (12.9%)	467 (10.7%)	360 (7.1%)	419 (6.3%)	326 (3.7%)
<b>Surfactant replacement</b>					
Number of times given	5,932	6,561	5,525	4,201	3,667
Number (%) of babies receiving	2,743 (83.2%)	3,258 (74.6%)	3,023 (60.0%)	2,677 (40.4%)	2,386 (27.0%)
<b>TPN</b>					
Number of days of care (over 14 days' use)	20,182	17,919	11,200	7,525	5,074
Number (%) of babies receiving	1,391 (42.2%)	1,411 (32.3%)	990 (19.7%)	692 (10.4%)	515 (5.8%)
<b>Palivizumab</b>					
Number of times given	90	103	52	31	14
Number (%) of babies receiving	77 (2.3%)	68 (1.6%)	38 (0.8%)	26 (0.4%)	12 (0.1%)
<b>ROP surgery</b>					
Number of surgeries	116	53	36	34	15
Number (%) of babies receiving	91 (2.8%)	45 (1.0%)	32 (0.6%)	30 (0.5%)	15 (0.2%)
<b>Neonatal surgery</b>					
Number of surgeries	291	283	203	175	169
Number (%) of babies receiving	255 (7.7%)	266 (6.1%)	185 (3.7%)	162 (2.4%)	161 (1.8%)

TPN: total parenteral nutrition, ROP: retinopathy or prematurity.\*19 babies had missing gestational age information.

**Table A5: Mean (SE) level of care cost per baby (2018/19 UK £) for very preterm babies in England over the period 2014-2018 using multiple imputation (n = 29,842)**

	<b>27 weeks gestation (n = 3,580)</b>	<b>28 weeks gestation (n = 4,674)</b>	<b>29 weeks gestation (n = 5,325)</b>	<b>30 weeks gestation (n = 6,979)</b>	<b>31 weeks gestation (n = 9,284)</b>
<b>Resource use item</b>	<b>Mean (SE) cost per baby</b>	<b>Mean (SE) cost per baby</b>	<b>Mean (SE) cost per baby</b>	<b>Mean (SE) cost per baby</b>	<b>Mean (SE) cost per baby</b>
<b>Level of daily care</b>					
Intensive care	£27,845 (£436)	£20,883 (£309)	£14,512 (£217)	£8,445 (£133)	£5,097 (£108)
High-dependency care	£27,212 (£386)	£19,284 (£292)	£11,486 (£198)	£7,788 (£135)	£5,112 (£82)
Special care without carer	£20,254 (£201)	£21,506 (£164)	£21,712 (£127)	£19,883 (£98)	£16,434 (£75)
Special care with carer	£762 (£22)	£829 (£22)	£825 (£20)	£850 (£18)	£832 (£15)
Normal care	£0 (£0)	£0.44 (£0.44)	£0 (£0)	£0.24 (£0.24)	£0.52 (£0.42)
<b>Total level of care costs</b>	<b>£76,072 (£613)</b>	<b>£62,502 (£461)</b>	<b>£48,534 (£326)</b>	<b>£36,966 (£222)</b>	<b>£27,475 (£159)</b>

SE: standard error



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