Outcomes in relation to early parenteral nutrition use in preterm neonates born between 30 and 33 weeks' gestation: a propensity score matched observational study

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ABSTRACT

Objective To evaluate whether in preterm neonates parenteral nutrition use in the first 7 postnatal days, compared with no parenteral nutrition use, is associated with differences in survival and other important morbidities. Randomised trials in critically ill older children show that harms, such as nosocomial infection, outweigh benefits of early parenteral nutrition administration; there is a paucity of similar data in neonates.

Design Retrospective cohort study using propensity matching including 35 maternal, infant and organisational factors to minimise bias and confounding.

Setting National, population-level clinical data obtained for all National Health Service neonatal units in England and Wales.

Patients Preterm neonates born between 30^{+0} and 32^{+6} weeks^{+days}.

Interventions The exposure was parenteral nutrition administered in the first 7 days of postnatal life; the comparator was no parenteral nutrition.

Main outcome measures The primary outcome was survival to discharge from neonatal care. Secondary outcomes comprised the neonatal core outcome set.

Results 16 292 neonates were compared in propensity score matched analyses. Compared with matched neonates not given parenteral nutrition in the first postnatal week, neonates who received parenteral nutrition had higher survival at discharge (absolute rate increase 0.91%; 95% CI 0.53% to 1.30%), but higher rates of necrotising enterocolitis (absolute rate increase 4.6%), bronchopulmonary dysplasia (absolute rate increase 3.9%), late-onset sepsis (absolute rate increase 1.5%) and need for surgical procedures (absolute rate increase 0.92%).

Conclusions In neonates born between 30^{+0} and 32^{+6} weeks' gestation, those given parenteral nutrition in the first postnatal week had a higher rate of survival but higher rates of important neonatal morbidities. Clinician equipoise in this area should be resolved by prospective randomised trials.

Trial registration number NCT03767634.

What is already known on this topic?

- Preterm neonates are among the highest users of parenteral nutrition.
- Randomised trials in critically ill older children show that harms, such as nosocomial infection, outweigh benefits of early parenteral nutrition administration.
- There is a paucity of similar randomised trial data in neonates.

What this study adds?

- Early parenteral nutrition use is associated with higher survival but higher morbidity.
- Trials focused on important outcomes are needed to determine which neonates benefit from early parenteral nutrition.

INTRODUCTION

Preterm birth abruptly ends the transplacental transfer of nutrients that support fetal growth. Preterm neonates have limited stores of energy, protein and other nutrients, and have difficulty tolerating adequate milk volumes immediately after birth.[1] Recognising this, preterm neonates are commonly given parenteral nutrition (PN) until enteral feeding is fully established. Neonatal PN was first described in 1968[2] and since then it has become widely used,[3] but the evidence is sparse. Specifically, the impact of administration of early compared with late initiation of PN has not been evaluated in randomised controlled neonatal trials powered for clinically meaningful endpoints.[4] Consequently, meta-analyses have not provided reliable recommendations for clinical practice.[5–7]

PN has known detrimental effects, in particular increased risk of bloodstream infection.[8] Recent evidence from large randomised controlled trials showed use of PN in critically unwell adults[9] and children[10] during the first week of admission to an intensive care unit led to worse outcomes when compared with delayed PN administration. Furthermore, a subgroup analysis of the paediatric population limited to term neonates showed increased rates of nosocomial infection with early PN use.[11] These studies highlight the uncertainty around the risks and benefits of PN administration in the early postnatal period. Additionally, the neonatal population is heterogeneous and the balance of risks and

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benefits is likely to vary according to gestational age and growth restriction. Thus, despite the limited evidence base and enduring uncertainty, the early initiation of PN in more preterm neonates is widely practised[12] and advised in national practice guidance[13]; therefore, conducting a randomised trial may be difficult in this population due to a lack of equipoise.[4]

Recognising these challenges, we undertook an observational study using population-level, routinely recorded clinical data. We selected preterm neonates born between 30^{+0} and 32^{+6} gestational weeks because routine early initiation of PN was not universally indicated in UK national guidance over the study period (January 2012–December 2017) for these infants, and hence nutritional practice varied. We used propensity scores to form matched comparator groups. The use of population-level data ensured this study was powered for clinically important outcomes.

OBJECTIVE

To evaluate if there was any difference in survival and other important neonatal outcomes in preterm neonates born between 30^{+0} and 32^{+6} weeks' gestation who did or did not receive PN in the first 7 postnatal days.

METHODS

We undertook a retrospective cohort study using quality-assured, routinely recorded neonatal clinical data available in a national database. We applied propensity score methodology to form matched subgroups of neonates with similar background characteristics, exposed to different PN strategies to compare their outcomes. We prospectively registered this study and published the study protocol.[14] All UK National Health Service (NHS) neonatal units in England and Wales agreed to the use of their data. A list of contributing neonatal units and their UK Neonatal Collaborative lead clinicians is provided (online supplemental etable 8).

Patients

We used de-identified data held in the National Neonatal Research Database (NNRD)[15] from all NHS neonatal units in England and Wales from 2012 onwards. The NNRD holds quality-assured, curated data sourced through extractions from point-of-care electronic health records completed by health professionals during clinical care.[16] The quality and completeness of the data held in the NNRD have been shown to be satisfactory for research[17] and no additional data cleaning was undertaken.

Study population

We used data from all neonates born between 30^{+0} and 32^{+6} weeks' gestational age between 1 January 2012 and 31 December 2017 and admitted to a neonatal unit in England and Wales. We excluded neonates with major congenital gastrointestinal malformations, life-limiting conditions or congenital conditions requiring surgery in the neonatal period (defined in online supplemental etable 1): they do not receive standard neonatal nutritional care and were expected to have different outcomes. We also excluded neonates in whom key background data (birth weight or gestational age) or primary outcome data were missing.

Intervention

The intervention was PN administered at any point in the first 7 days of postnatal life. This threshold was based on the previous randomised trials in adult and paediatric intensive care populations.[9 10] We defined the 'PN' group as infants who received PN in any volume, of any type (standardised or tailor-made), by any route (peripheral intravenous cannula or central venous catheter) for any duration during the first 7 postnatal days. The comparator group—the 'No PN' group—comprised eligible neonates not recorded to have received any PN in the first 7 days.

Outcomes

The primary outcome was survival to discharge from neonatal care; secondary outcomes were other components of the neonatal core outcomes set[18] and growth (online supplemental etable 2). Neonatal core outcomes are those considered essential for neonatal research by former patients, parents, clinicians and researchers.[19] Growth was included as a widely cited justification for administering PN to neonates to improve growth and theoretically optimise long-term outcomes.[20] As measures for the core outcomes have not been defined, established definitions were used (online supplemental etable 2). The following core outcome set components were not reported as relevant data are not captured in the NNRD: quality of life, gross motor ability and cognitive ability. After the prespecified analyses showed opposing effects of PN on mortality and morbidity, post-hoc analyses investigating the effect of PN on death or each secondary outcome were undertaken to explore whether any increased morbidity seen in a treatment group was solely due to increased survival.

Statistical analysis

We calculated that 12 000 neonates were required in each group to have 90% power to detect an absolute difference in survival to discharge of 1.3% (two-sided significance of 5%); the expected difference was calculated using a baseline mortality rate of 3.4%[21] and an OR of 0.73 for early versus late PN suggested by previous research.[10]

To minimise bias by confounding, we used propensity matching with logistic regression. Infants were initially matched on gestational week at birth (three groups) and whether or not they were small for gestational age defined as <10th centile for gestational age at birth (two groups) as these were identified a priori as critically important variables. Within the six groups this created, further matching was then undertaken using propensity score (split by decile). The propensity score included maternal, infant and organisational factors. Infant factors were those occurring at birth and on the first postnatal day, preceding the decision to administer PN (online supplemental file etable 3). We then identified pairs of matched neonates who differed on exposure to PN. We calculated absolute risk differences and ORs for the prespecified, dichotomous outcomes for the two groups. We used the Holm-Bonferroni method[22] when analysing secondary outcomes to avoid erroneous inferences due to multiple comparisons.

To minimise the risk confounding due to hidden bias affecting the findings, we undertook a planned sensitivity analysis. We constructed a dichotomous variable and calculated the magnitude of imbalance between the two groups required to stack the odds against the superior treatment option; we then compared this with the imbalance in observed background variables to assess whether it was plausible such as an unobserved variable existed.[23] This models a 'worst-case' scenario in which an unobserved background variable provided an alternative explanation for the significant differences in outcomes between the two groups.

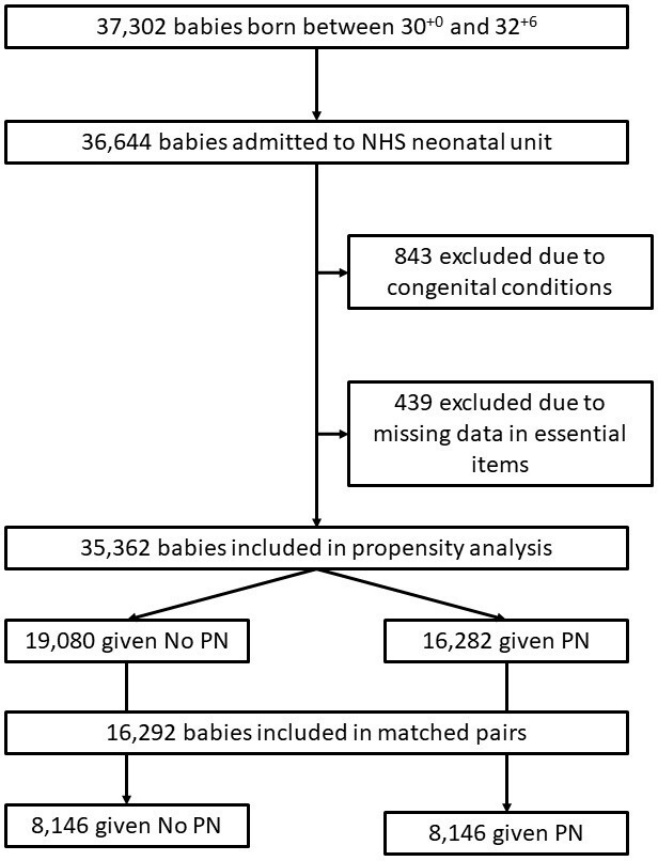

Figure 1 Participant flow for the primary analysis. NHS, National Health Service; PN, parenteral nutrition.

Deviations from protocol

Two deviations from the published protocol occurred. The first related to the use of data from neonates born in Scotland: this required authorisation from the Scottish Public Benefit and Privacy Panel,[24] which we did not obtain in sufficient time. Therefore, we completed the project using data from neonates born in England and Wales. The second involved post-hoc analyses of the effect of PN on composite outcomes, combining death or each secondary outcome, as described above: this was the only analysis that was not prespecified.

RESULTS

Over the study period, there were 37 302 births in this cohort: 36 644 neonates were admitted to an NHS neonatal unit in England or Wales.

We excluded 843 neonates due to congenital conditions, 439 due to missing data, leaving 35 362 included in the propensity score analysis with 8146 matched pairs (figure 1).

In the cohort before matching, 16 282 neonates received PN in the first 7 days and 19 080 did not. The population given PN had a lower gestational age and lower birth weight. They also had higher rates of interventions after birth (table 1). After matching, no major differences were seen: the 8146 pairs were well matched on all background variables (table 1, online supplemental etable 4 and efigure 1).

The survival rate for the cohort before matching was 98.6%. After matching, the PN group had a higher rate of survival (98.9% vs 98.0%; absolute rate difference 0.91%, 95% CI 0.53% to 1.30%). The PN group had higher rates of bronchopulmonary dysplasia, late-onset sepsis, necrotising enterocolitis and need for surgical procedures after correcting for multiple comparisons (table 2). The largest effects associated with PN were a 4.6% higher rate of necrotising enterocolitis (absolute rate: 8.1% vs 3.5%: 95% CI for difference 3.9% to 5.3%) and a 3.9% higher rate of bronchopulmonary dysplasia (absolute rate: 7.7% vs 3.8%: 95% CI for difference 3.2% to 4.7%). The PN group had a lower weight at discharge with an absolute difference in mean Z-score of 0.12 (95% CI 0.10 to 0.15). We undertook post-hoc analyses to examine the association between PN use and a composite of death or each morbidity separately. The PN group had a higher proportion of neonates with 'death or bronchopulmonary dysplasia' (absolute rate: 8.5% vs 5.8%) and 'death or necrotising enterocolitis' (absolute rate: 8.7% vs 5.6%) (online supplemental etable 1).

For several outcomes, there were large amounts of missing data (table 2). This was an issue for the 2-year outcome components impaired ability to walk, blindness or visual impairment, and deafness or hearing impairment, where over 85% of data were missing. In addition, as discharge head circumference data

Table 1 Key background characteristics of neonates

	Entire cohort		Matched cohort	
	No PN group (N=19 080)	PN group (N=16 282)	No PN group (N=8146)	PN group (N=8146)
Gestational age (weeks), mean (SD)	31.5 (0.7)	30.9 (0.8)	31.2 (0.8)	31.2 (0.8)
Birth weight (kg), mean (SD)	1.74 (0.28)	1.47 (0.32)	1.67 (0.28)	1.59 (0.29)
Birth weight Z-score, mean (SD)	0.12 (0.95)	−0.16 (1.0)	0.01 (0.91)	−0.05 (0.88)
Proportion small for gestational age, n (%)	834 (4.4)	3773 (23.2)	710 (8.7)	715 (8.8)
Female, n (%)	8787 (46.1)	7424 (45.6)	3664 (45.0)	3733 (45.8)
Maternal factors				
Maternal age, mean (SD)	30.5 (6.3)	30.7 (6.3)	30.8 (6.3)	30.8 (6.2)
Maternal complications of pregnancy*, n (%)	14 025 (73.5)	12 234 (75.1)	6055 (74.3)	6177 (75.8)
Complete course of antenatal steroids, n (%)	3312 (18.2)	2515 (16.1)	1328 (17.0)	1324 (17.0)
Infant factors after birth				
Apgar score at 5 min, median (IQR)	9 (8–10)	9 (8–9)	9 (8–10)	9 (8–10)
Intubation during resuscitation, n (%)	1730 (9.1)	3275 (20.1)	1175 (14.4)	1180 (14.5)
Infant factors on first day				
Admission temperature, mean (SD)	36.7 (0.6)	36.7 (0.6)	36.8 (0.6)	36.8 (0.6)
Admission heart rate, mean (SD)	156 (18.0)	157 (18.2)	157 (18.0)	157 (18.1)
Admission oxygen saturation, mean (SD)	93.4 (7.8)	93.6 (7.6)	93.3 (7.8)	93.3 (7.8)
Ventilated on first day, n (%)	2833 (14.9)	5364 (33.1)	1932 (23.8)	1979 (24.4)
Inotropes on first day, n (%)	186 (1.0)	658 (4.1)	128 (1.6)	149 (1.8)
Treated for infection on first day, n (%)	8487 (44.5)	7795 (47.9)	3837 (47.1)	3843 (47.2)
Enteral feeding on first day, n (%)	14 401 (75.5)	8593 (52.8)	4570 (56.1)	4555 (55.9)
Organisational factors				
Born in level 3 unit (NICU), n (%)	7963 (41.7)	7294 (44.8)	3525 (43.3)	3463 (42.5)
Transferred on first day, n (%)	810 (4.2)	1112 (6.8)	450 (5.5)	464 (5.7)

*'Maternal complications of pregnancy' includes gestational hypertension, pre-eclampsia, diabetes, gestational diabetes, prolonged rupture of membranes or suspected chorioamnionitis.
NICU, neonatal intensive care unit; PN, parenteral nutrition.

Table 2 Neonatal outcomes

	Entire cohort				Matched cohort					
	No PN group (N=19 080)		PN group (N=16 282)		No PN group (N=8146)		PN group (N=8146)			
		Missing data		Missing data		Missing data		Missing data	Treatment effect (95% CI)	P value
Survival, n (%)	18 838 (98.7)	0	16 059 (98.6)	0	7987 (98.0)	0	8057 (98.9)	0	0.91 (0.53 to 1.30)	<0.001*
Secondary outcomes: outcomes during admission										
Brain injury on imaging, n (%)	88 (0.5)	0†	182 (1.1)	0†	48 (0.59)	0†	73 (0.90)	0†	0.31 (0.05 to 0.57)	0.02
Bronchopulmonary dysplasia, n (%)	525 (2.8)	354	1923 (12.0)	234	302 (3.8)	198	619 (7.7)	106	3.9 (3.2 to 4.7)	<0.001*
Late-onset sepsis, n (%)	108 (0.6)	0†	441 (2.7)	0†	59 (0.73)	0†	179 (2.2)	0†	1.5 (1.1 to 1.8)	<0.001*
Necrotising enterocolitis, n (%)	521 (2.7)	0†	1518 (9.3)	0†	285 (3.5)	0†	660 (8.1)	0†	4.6 (3.9 to 5.3)	<0.001*
Need for surgical procedures, n (%)	123 (0.6)	0†	358 (2.2)	0†	69 (0.85)	0†	147 (1.8)	0†	0.92 (0.57 to 1.3)	<0.001*
Retinopathy of prematurity, n (%)	410 (4.9)	10 728	879 (6.9)	3504	272 (5.3)	3007	297 (5.4)	2642	0.12 (−0.73 to 0.97)	0.78
Seizures, n (%)	107 (0.6)	14	214 (1.3)	37	81 (0.99)	3	114 (1.4)	8	0.39 (0.06 to 0.72)	0.02
Weight Z-score, mean (SD)	0.12 (0.95)	245	−0.16 (1.0)	170	0.073 (0.98)	134	−0.024 (0.96)	77	−0.12 (−0.10 to −0.15)	<0.001*
Secondary outcomes: outcomes at 2 years										
Impaired ability to walk, n (%)	62 (3.9)	17 481	127 (4.4)	13 371	41 (4.1)	7157	44 (3.8)	6994	−0.25 (−1.9 to 1.4)	0.77
Blindness or visual impairment, n (%)	91 (5.8)	17 516	178 (6.2)	13 414	54 (5.5)	7173	73 (6.4)	7009	0.83 (−1.2 to 2.9)	0.42
Deafness or hearing impairment, n (%)	23 (1.5)	17 530	56 (2.0)	13 436	13 (1.4)	7183	19 (1.7)	7022	0.31 (−0.76 to 1.4)	0.57

*Indicates a statistically significant result (p<0.05). Secondary outcomes corrected for multiple comparisons using Holm-Bonferroni method.
†Amount of missing data uncertain as absence of data interpreted as absence of outcome.
PN, parenteral nutrition.

were almost universally missing: this outcome was not analysed. Due to the format in which data are entered into the electronic patient record for the outcomes brain injury on imaging, late-onset sepsis, necrotising enterocolitis and need for surgical procedures, absence of a response was assumed to be lack of the condition: it is not possible to know how much data were missing.

The sensitivity analysis showed the magnitude of imbalance required for an unrecorded background variable to account for the differences found (online supplemental etable 5) was only exceeded by a minority of the background variables before matching (online supplemental etable 6).

DISCUSSION

In this matched observational study of neonates born between 30^{+0} and 32^{+6} weeks' gestation, those given PN during the first postnatal week had higher survival compared with neonates not given PN. However, neonates given PN had higher rates of bronchopulmonary dysplasia, late-onset sepsis, necrotising enterocolitis and need for surgical procedures. They also had a lower weight for gestation SD score at discharge.

The finding of higher survival in neonates given PN in the first postnatal week contrasts with the results of a randomised trial in critically unwell older children[10] and the subsequent subgroup analysis of term neonates,[11] where no difference in mortality was found. Similar randomised data for preterm neonates are not available, but our finding should be interpreted with caution as in this observational study, residual confounding cannot be excluded.[25] It remains possible clinicians withheld PN from very ill babies, even though the study cohorts were well matched on all recorded variables. There are plausible biological mechanisms that could explain the higher survival in neonates given PN. Nutritional deficits are common in the first postnatal week, particularly in more preterm infants, and this period is also when the majority of neonatal deaths occur.[26] Early PN initiation is intended to decrease catabolism which may, in this period, be crucial for survival. The difference in survival is small in absolute terms (0.9%), but given the mortality in this population equates to a 50% reduction in relative risk of mortality and thus warrants further investigation.

We also find neonates given PN have higher rates of important neonatal morbidities, particularly bronchopulmonary dysplasia and necrotising enterocolitis. Harmful effects are plausible, such as systemic pro-inflammatory changes triggered by PN proposed as a mechanism causing bronchopulmonary dysplasia[27] and necrotising enterocolitis.[24] PN use soon after an insult such as preterm birth may impair tissue healing by directly inhibiting autophagy.[28] Neonates given PN also had a lower weight for gestation SD score at discharge. This is in keeping with previous meta-analyses which have failed to find consistent evidence that

PN use increases growth.[5 6] Administration of PN might also influence clinician decision around enteral feeding and reduce milk intake. Lack of enteral substrate exacerbates the risk of necrotising enterocolitis.[29 30]

A strength of this work is that we followed prespecified analyses which were detailed in the prospectively published protocol. A further strength is that by combining propensity score matching and the extensive background data held in the NNRD on both the neonates and their mothers,[17 30] we generated two well-matched cohorts, approximating the effect of prospective randomisation and minimising the risk of confounding. The database used enabled us to study a complete population of size sufficient for analyses of associations of PN and rare outcomes. Previous PN trials in neonates have been powered for short-term surrogate outcomes, and the lack of data on clinically meaningful outcomes has prevented Cochrane reviews from making recommendations for practice.[5–7] We limited the risk of false discovery associated with multiple comparisons[31] by using the Holm-Bonferroni method.

The major limitation of this comparative study is that the intervention was not randomly assigned: confounding is a possibility[32] as other elements of care were not standardised or equally balanced as in a rigorous randomised controlled trial. We undertook a sensitivity analysis to explore whether confounding due to an unmeasured variable was possible as propensity score matching only balances measured variables. This showed the magnitude of imbalance required in a hypothetical missing variable was similar to the imbalance seen in variables like the Apgar score at 5 min or whether a neonate was transferred. Another limitation relates to missing data in the matched babies: we were able to quantify the degree of missingness for some data items, for other items it was not possible. For the 2-year outcomes, over 85% of data were missing, meaning no firm conclusions could be drawn. For other outcomes, it is not known how much data were missing and comparison with published data is difficult due to differences in how populations and outcomes are defined. Analyses of the NNRD show a rate of brain injury comparable with other published reports,[33] and data for outcomes including necrotising enterocolitis and sepsis are used for national audit and benchmarking.[34]

The overall findings that PN use is associated with higher survival, but also with higher rates of important neonatal morbidities, reflect the complex effects this intervention has in preterm neonates. The balance of risk to benefit is likely to vary by gestation and degree of growth restriction: to show how these balance in vivo prospective, randomised controlled trials adequately powered for important neonatal outcomes in relevant subgroups should be undertaken.[35] Previously, it was felt that further randomised trials would not be possible due to lack of clinician equipoise,[4] but our results show such research is essential.

CONCLUSION

In this matched study of neonates born between 30^{+0} and 32^{+6} weeks' gestation, those given PN in the first postnatal week had a higher rate of survival but also higher rates of necrotising enterocolitis, sepsis and bronchopulmonary dysplasia. This study provides evidence of important uncertainty around the benefits and risks of PN which should be addressed in prospective randomised trials.

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Contributors JWHW, NM and CG conceived this project. JWHW, NL, SNU and CG planned the statistical analyses. Data were extracted from the NNRD by KO and checked by CB. Data analysis was undertaken by JWHW and NL. The first draft of the manuscript was written by JWHW and revised by CG. NL, CB, KO, SNU and NM edited and reviewed the manuscript. It was approved by JWHW, NL, CB, KO, SNU, NM and CG.

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Competing interests JWHW has received support from Chiesi Pharmaceuticals to attend an educational conference and has received a research grant from Mason Medical Research Foundation. SNU has received funding from the National Institute of Health Research, the Department of Health and Prolacta Life Sciences. SNU has been on the Advisory Board of Fresenius Kabi and received honoraria and travel expenses for speaking at study days organised by Fresenius Kabi. SNU is a member of the National Institute for Health and Care Excellence Parenteral Nutrition Guideline Development Committee. NM is the Chief Investigator for the National Neonatal Research Database and Director of the Neonatal Data Analysis Unit at Imperial College London. In the last 5 years, NM has served on the Board of Trustees of the Royal College of Paediatrics and Child Health, David Harvey Trust, Medical Women's Federation and Medact; and is a member of the Nestle Scientific Advisory Board. NM has received research grants from the British Heart Foundation, Medical Research Council, National Institute of Health Research, Westminster Research Fund, Collaboration for Leadership in Applied Health and Care Northwest London, Healthcare Quality Improvement Partnership, Bliss, Prolacta Life Sciences, Chiesi, Shire and HCA International; travel and accommodation expenses from Nutricia, Prolacta, Nestle and Chiesi; honoraria from Ferring Pharmaceuticals and Alexion Pharmaceuticals for contributions to expert advisory boards, and Chiesi for contributing to a lecture programme. CG is part of an international team developing reporting guidance (a CONSORT extension) for clinical trials using cohorts and routinely collected health data. He has received support from Chiesi Pharmaceuticals to attend an educational conference; in the past 5 years he has been an investigator on received research grants from Medical Research Council, National Institute of Health Research, Canadian Institute of Health Research, Department of Health in England, Mason Medical Research Foundation, Westminster Medical School Research Trust and Chiesi Pharmaceuticals, and has been an unremunerated member of the Neonatal Data Analysis Unit Board, which oversees the NNRD.

Patient consent for publication Not applicable.

Ethics approval This study only used de-identified data from the NNRD. The NNRD is a UK Research Ethics Committee-approved (REC Reference: 16/LO/1093) and Confidentiality Advisory Group-approved (ECC 8-05(f/2010)) national data asset. All data were stored on NHS servers. Parents can opt out of their baby's data being held within the NNRD. Study-specific REC approval and Health Research Authority and Health and Care Research Wales approval was obtained (18/NI/0214). Approval for inclusion of data from their centres in this study was obtained from all English and Welsh neonatal units. A list of all contributing neonatal units and their UK Neonatal Collaborative lead clinicians is provided (online supplemental table 8).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The NNRD is a national Data Asset discoverable through the Health Data Research UK Alliance Innovation Gateway (https://www.healthdatagateway.org/) and is available for use by external investigators. Data from this study is available from the Neonatal Data Analysis Unit upon reasonable request.

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Online only supplemental material

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eTable 1: Exclusion criteria: major congenital gastrointestinal malformations, conditions requiring surgery in the neonatal period or life-limiting conditions

Clevermed code	ICD-10 code	Diagnosis
10741	Q39.0	Oesophageal atresia without distal fistula
16195	Q39.0	Atresia of oesophagus without fistula
10740	Q39.1	Oesophageal atresia with distal trache-oesophageal fistula
16196	Q39.1	Atresia of oesophagus with trache-oesophageal fistula (TOF)
16197	Q39.2	Congenital trache-oesophageal fistula without atresia (TOF)
10273	Q39.3	Congenital stenosis of the oesophagus
16198	Q39.3	Congenital stenosis and stricture of oesophagus
16199	Q39.4	Oesophageal web
10358	Q41.0	Duodenal atresia / stenosis / web (specify)
16212	Q41.0	Congenital absence, atresia and stenosis of duodenum
16213	Q41.0DA	Duodenal atresia / stenosis
10605	Q41.1	Jejunal atresia / stenosis (specify)
16214	Q41.1JA	Jejunal atresia / stenosis
10541	Q41.2	Ileal atresia / stenosis (specify)
16215	Q41.2	Congenital absence, atresia and stenosis of ileum
16216	Q41.2IA	Ileal atresia / stenosis
16217	Q41.X	Congenital absence, atresia and stenosis of small intestine
16218	Q42.0	Congenital absence, atresia and stenosis of rectum with fistula
10496	Q42.00	High anorectal anomaly with rectourethral fistula
10497	Q42.01	High anorectal anomaly with rectovesical fistula
10498	Q42.02	High anorectal anomaly with rectovulval fistula
10495	Q42.03	High anorectal anomaly with rectocutaneous fistula
10494	Q42.04	High anorectal anomaly with rectocloacal fistula
10493	Q42.08	High anorectal anomaly with fistula (specify)
10499	Q42.1	High anorectal anomaly without fistula
16219	Q42.1	Congenital absence, atresia and stenosis of rectum without fistula
16220	Q42.2	Congenital absence, atresia and stenosis of anus with fistula
10636	Q42.20	Low anorectal anomaly with anocutaneous fistula
10637	Q42.21	Low anorectal anomaly with anovestibular fistula
10638	Q42.28	Low anorectal anomaly with fistula (other specify)
10639	Q42.3	Low anorectal anomaly without fistula
16221	Q42.3	Congenital absence, atresia and stenosis of anus without fistula
10240	Q42.31	Congenital anal stenosis
16222	Q42.8	Congenital absence, atresia and stenosis of anus of other parts of large intestine
16223	Q429	Congenital absence, atresia and stenosis of anus of large intestine, part unspecified
16224	Q42X	Congenital absence, atresia and stenosis of large intestine
16235	Q43.7	Persistent cloaca
15890	Q00.0	Anencephaly

15891	Q00.1	Craniorachischisis
15892	Q00.2	Iniencephaly
15893	Q00.X	Anencephaly and similar malformations
15894	Q01.0	Frontal encephalocele
15895	Q01.1	Nasofrontal encephalocele
15896	Q01.2	Occipital encephalocele
15897	Q01.8	Encephalocele of other sites
15898	Q01.9	Encephalocele (unknown or unspecified cause)
15899	Q01.X	Encephalocele
15918	Q04.2	Holoprosencephaly
15926	Q05.0	Cervical spina bifida with hydrocephalus
15927	Q05.1	Thoracic spina bifida with hydrocephalus
15928	Q05.2	Lumbar spina bifida with hydrocephalus
15929	Q05.3	Sacral spina bifida with hydrocephalus
15930	Q05.4	(unknown or unspecified cause) spina bifida with hydrocephalus
15931	Q05.5	Cervical spina bifida without hydrocephalus
15932	Q05.6	Thoracic spina bifida without hydrocephalus
15933	Q05.7	Lumbar spina bifida without hydrocephalus
15934	Q05.8	Sacral spina bifida without hydrocephalus
15935	Q05.9	Spina bifida (unknown or unspecified cause)
10986	Q05.9a	Spina bifida
10704	Q05.9b	Myelomeningocele (specify site)
15936	Q05.X	Spina bifida
16024	Q20.0	Common arterial trunk (Truncus malformation)
10356	Q20.1	Double outlet right ventricle (DORV)
16025	Q20.1	Double outlet right ventricle (DORV)
16026	Q20.2	Double outlet left ventricle (DOLV)
11070	Q20.3	Transposition of the great vessels (TGA)
16027	Q20.3	Transposition great arteries (TGA)
16028	Q20.4	Double inlet ventricle (DILV)
16029	Q20.5	Discordant atrioventricular connection
16030	Q20.6	Isomerism of atrial appendages
16031	Q20.8	Other cong malforms of cardiac chambers and connections
16032	Q20.9	Cong malforms of cardiac chambers and connections unspec
16033	Q20.X	Congenital malformations of cardiac chambers and connections
16035	Q20.91	Atrium single
16036	Q20.92	Ventricle single
10097	Q21.2	Atrio-ventricular septal defect (AVSD)
16039	Q21.2	Atrioventricular septal defect (AVSD)
11043	Q21.3	Tetralogy of Fallot
16040	Q21.3	Tetralogy of Fallot

16045	Q22.0	Pulmonary valve atresia
16046	Q22.1	Congenital pulmonary valve stenosis
16047	Q22.2	Congenital pulmonary valve insufficiency
16048	Q22.3	Other congenital malformations of pulmonary valve
16049	Q22.4	Congenital tricuspid atresia / stenosis
16050	Q22.5	Ebstein's anomaly
16051	Q22.6	Hypoplastic right heart syndrome
16052	Q22.8	Other congenital malformations of tricuspid valve
16053	Q22.9	Congenital malformation of tricuspid valve (unknown or unspecified cause)
16054	Q22.X	Congenital malformations of pulmonary and tricuspid valves
16055	Q23.0	Congenital stenosis of aortic valve (AS)
16056	Q23.1	Congenital insufficiency of aortic valve
16057	Q23.2	Congenital mitral stenosis (MS)
16058	Q23.3	Mitral atresia
16059	Q23.4	Hypoplastic left heart syndrome (HLH)
16060	Q23.8	Other congenital malformations of aortic and mitral valves
16061	Q23.9	Congenital malformation of aortic and mitral valves unspec
16062	Q23.X	Congenital malformations of aortic and mitral valves
16079	Q25.1	Coarctation of aorta
10227	Q25.19	Coarctation of the aorta
16080	Q25.2	Hypoplasia of aortic arch
16081	Q25.3	Stenosis of aorta (AS)
16082	Q25.4	Malformation of aorta
16083	Q25.5	Atresia of pulmonary artery
16084	Q25.6	Stenosis of pulmonary artery (PS)
16086	Q25.8	Other congenital malformations of great arteries
16087	Q25.8	Transposition of the great vessels (TGA)
11057	Q26.2	Total anomylous pulmonary venous drainage (TAPVD)
16092	Q26.2	Total anomalous pulmonary venous connection (TAPVD)
16154	Q33.6	Hypoplasia and dysplasia of lung
16241	Q44.2	Atresia of bile ducts
10123	Q60.1	Bilateral renal agenesis
16318	Q60.1B	Renal agenesis, bilateral
16324	Q60.6	Potter's syndrome
16327	Q61.1	Polycystic kidney, infantile type
10100	Q61.1a	Autosomal recessive polycystic kidney – infantile
10367	Q64.1	Ectopia vesicae
16356	Q64.1	Exstrophy of urinary bladder
10854	Q64.2	Posterior urethral valves (PUV)
16357	Q64.2	Congenital posterior urethral valves (PUV)
16360	Q64.5	Congenital absence of bladder and urethra

10008	Q64.5a	Absence of bladder
10236	Q64.5b	Congenital absence of urethra
16475	Q77.1	Thanatophoric short stature
10246	Q79.0	Congenital diaphragmatic hernia
10490	Q79.0	Hernia into the cord
16495	Q79.0	Congenital diaphragmatic hernia
16496	Q79.1A	Aplasia of diaphragm
16497	Q79.1E	Eventration of diaphragm
16498	Q79.2	Exomphalos
10395	Q79.2	Exomphalos
16499	Q79.3	Gastroschisis
16589	Q90.0	Trisomy 21, meiotic nondisjunction
16590	Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
16591	Q90.2	Trisomy 21, translocation
16592	Q90.9	Down's syndrome (unknown or unspecified cause)
16593	Q90.X	Down's syndrome
16594	Q91.0	Trisomy 18, meiotic nondisjunction
16595	Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
16596	Q91.2	Trisomy 18, translocation
16597	Q91.3	Edwards' syndrome (unknown or unspecified cause)
16598	Q91.4	Trisomy 13, meiotic nondisjunction
16599	Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
16600	Q91.6	Trisomy 13, translocation
16601	Q91.7	Patau's syndrome (unknown or unspecified cause)
16602	Q91.X	Edwards' syndrome and Patau's syndrome

eTable 2: Outcome definitions

Outcome	Definition
Late-Onset Sepsis	Defined in line with the Royal College of Paediatrics and Child Health National Neonatal Audit Programme (NNAP) definition as "pure growth of a pathogen from blood" or "pure growth of a skin commensal with three or more clinical signs" or a "mixed growth with three or more clinical signs" after the first 72 hours, during the neonatal admission
Necrotising enterocolitis	Defined in line with the Royal College of Paediatrics and Child Health NNAP definition. Necrotising enterocolitis may be diagnosed at surgery, post-mortem or on the basis of the following clinical and radiographic signs: at least one clinical feature from (i) Bilious gastric aspirate/emesis (ii) Abdominal distension (iii) Occult/gross blood in stool (no fissure) and at least one radiographic feature from: (i) Pneumatosis (ii) Hepatobiliary gas (iii) Pneumoperitoneum. As this definition was introduced in 2016 for babies born prior to this the following alternative definition was used; necrotising enterocolitis defined as recorded as receiving treatment for necrotising enterocolitis, or a recorded diagnosis of necrotising enterocolitis in an infant that received at least five consecutive days of antibiotic treatment while kept nil by mouth
Brain injury on imaging	Defined as a documented diagnosis of intraventricular haemorrhage (grade 3-4) or cystic periventricular leukomalacia during the neonatal admission
Retinopathy of prematurity	Defined as any retinopathy of prematurity recorded on routine screening in the NDS "retinopathy of prematurity ad-hoc form"
Bronchopulmonary dysplasia	Defined in line with the Royal College of Paediatrics and Child Health NNAP definition of severe bronchopulmonary dysplasia "receiving respiratory support at 36 weeks corrected gestational age"
Need for surgical procedures	Defined as any record of surgical procedure during the neonatal admission
Seizures	Defined as any recorded seizures or diagnosis of seizure disorder during the neonatal admission
Growth	Head circumference and weight, and standard deviation score of the head circumference and weight for postmenstrual age at discharge; head circumference velocity and weight velocity, and change in standard deviation score of the head circumference and weight for postmenstrual age from birth to discharge

Blindness	Defined as an answer of Yes to the question “Does this child have a visual impairment?” at two years of age
Deafness	Defined as an answer of Yes to the question “Does this child have a hearing impairment?” at two years of age
Ability to walk	Defined as an answer of Yes to the question “Is this child unable to walk without assistance?” at two years of age

eTable 3: Data fields extracted from the National Neonatal Research Database

Treatment	
Variable	**Data items**
Parenteral nutrition	**PN group** defined as Any of the following items entered in the 'Daily Care Fluids' and 'Feeding' during the first 7 days: • Y entry for PARENTERAL NUTRITION RECEIVED INDICATOR Or The following drug code entered in the Daily care medication during the first 7 days: • 1010238 Total parenteral nutrition **No PN group** defined as All other babies

Background variables for matching	
Variable	**Data items**
Gestational age at birth	**30^{+0} to 30^{+6} group** defined as Any of the following items entered in the GESTATION LENGTH (AT DELIVERY): • 30^{+0}, 30^{+1}, 30^{+2}, 30^{+3}, 30^{+4}, 30^{+5}, 30^{+6} **31^{+0} to 31^{+6} group** defined as Any of the following items entered in the GESTATION LENGTH (AT DELIVERY): • 31^{+0}, 31^{+1}, 31^{+2}, 31^{+3}, 31^{+4}, 31^{+5}, 31^{+6} **32^{+0} to 32^{+6} group** defined as Any of the following items entered in the GESTATION LENGTH (AT DELIVERY): • 32^{+0}, 32^{+1}, 32^{+2}, 32^{+3}, 32^{+4}, 32^{+5}, 32^{+6}
Small for gestational age	**Small for gestational age group** defined as Any result entered in the BIRTH WEIGHT which is below the 10^{th} centile on the UK-WHO growth chart **Appropriate for gestational age group** defined as All other babies

Background variables for propensity score matching	
Variable	**Data items**
Sex	Data will be extracted from PERSON PHENOTYPIC SEX • Categorical: 1 Male / 2 Female / 9 Indeterminate (unable to be classified as either male or female)
Multiplicity	Data will be extracted from NUMBER OF FETUSES (NOTED DURING PREGNANCY EPISODE); this excludes fetus papyraceous and fetuses reabsorbed in utero and not delivered.
Year of birth	Data will be extracted from DATE TIME OF BIRTH • Continuous in one-year bands
Maternal age	Data will be extracted from YEAR OF BIRTH (MOTHER) • Continuous variable
Maternal diabetes	Data will be extracted from MATERNITY COMPLICATING MEDICAL DIAGNOSIS TYPE (NATIONAL NEONATAL DATA SET) • Dichotomous: 08 Y/N

Background variables for propensity score matching	
Maternal gestational diabetes	Data will be extracted from MATERNITY OBSTETRIC DIAGNOSIS TYPE (CURRENT PREGNANCY) • Dichotomous: 06 Gestational diabetes mellitus Y/N
Maternal severe pre-eclampsia requiring pre-term birth	Data will be extracted from MATERNITY OBSTETRIC DIAGNOSIS TYPE (CURRENT PREGNANCY) • Dichotomous: 01 Severe pre-eclampsia requiring pre-term birth Y/N
Maternal severe pre-eclampsia	Data will be extracted from MATERNITY OBSTETRIC DIAGNOSIS TYPE (CURRENT PREGNANCY) • Dichotomous: 20 Severe pre-eclampsia Y/N
Maternal gestational hypertension	Data will be extracted from MATERNITY OBSTETRIC DIAGNOSIS TYPE (CURRENT PREGNANCY) • Dichotomous: 07 Gestational hypertension Y/N
Maternal prolonged rupture of membranes	Data will be extracted from NUMBER OF MINUTES (BIRTH TO EVENT) • Continuous variable
Maternal suspected chorioamnionitis	Data will be extracted from SIGNIFICANT MATERNAL PYREXIA IN LABOUR INDICATOR or INTRAPARTUM ANTIBIOTICS GIVEN INDICATOR • Dichotomous: Suspected chorioamnionitis defined as Y in either field • Dichotomous: No suspected chorioamnionitis defined as N in both fields
Maternal receipt of antenatal steroids	Data will be extracted from STEROIDS GIVEN DURING PREGNANCY TO MATURE FETAL LUNGS INDICATOR (Y/N) and ANTENATAL STEROID COURSE COMPLETION STATUS • Categorical: Complete course defined as Y and 1 Complete course • Categorical: Incomplete course defined as Y and 2 Incomplete course • Categorical: No steroids defined as N
Maternal receipt of antenatal magnesium sulphate	Data will be extracted from MOTHER RECEIVED MAGNESIUM SULPHATE IN 24 HOURS PRIOR TO DELIVERY • Dichotomous: Y/N
Infant Apgar score at 5 minutes	Data will be extracted from the APGAR SCORE (5 MINUTES) • Categorical: 0-10
Infant: chest compressions administered	Data will be extracted from NEONATAL RESUSCITATION METHODS (NATIONAL NEONATAL DATA SET) • Dichotomous: 16 Cardiac massage (Y/N)
Infant: Emergency resuscitation drugs administered	Data will be extracted from NEONATAL RESUSCITATION METHODS (NATIONAL NEONATAL DATA SET) • Dichotomous: 17 Adrenaline or 88 Any other drug (Y/N)
Infant: Intubated at resuscitation	Data will be extracted from NEONATAL RESUSCITATION METHODS (NATIONAL NEONATAL DATA SET) • Dichotomous: 15 Intubation (Y/N)
Infant: Surfactant administered	Data will be extracted from SURFACTANT GIVEN INDICATOR (DURING RESUSCITATION) • Dichotomous: Y/N
Infant: Umbilical cord pH	Data will be extracted from the UMBILICAL CORD BLOOD PH LEVEL (ARTERIAL) • Continuous: Arterial cord pH (6.00-8.00) Or if unavailable use: UMBILICAL CORD BLOOD PH LEVEL (VENOUS) • Continuous: Venous cord pH (6.00-8.00)
Infant: Admission temperature	Data will be extracted from TEMPERATURE (ON ADMISSION TO NEONATAL CRITICAL CARE) • Continuous

Background variables for propensity score matching	
Infant: Admission mean blood pressure	Data will be extracted from MEAN ARTERIAL BLOOD PRESSURE (ON ADMISSION TO NEONATAL CRITICAL CARE) • Continuous: 10-150
Infant: Admission blood glucose	Data will be extracted from BLOOD GLUCOSE CONCENTRATION (ON ADMISSION TO NEONATAL CRITICAL CARE) • Continuous: 0.0-50.0
Infant: Admission heart rate	Data extracted from HEART RATE (ON ADMISSION TO NEONATAL CRITICAL CARE) • Continuous: 50-350
Infant: Admission respiratory rate	Data extracted from RESPIRATORY RATE (ON ADMISSION TO NEONATAL CRITICAL CARE) • Continuous: 10-200
Infant: Admission oxygen saturation	Data extracted from OXYGEN SATURATION (ON ADMISSION TO NEONATAL CRITICAL CARE) • Continuous: 10-100
Infant: Surfactant administered on the first day	Data extracted from SURFACTANT GIVEN INDICATOR (ON NEONATAL CRITICAL CARE DAILY CARE DATE) • Continuous: Y/N
Infant: Mechanical ventilation on the first day	Data extracted from RESPIRATORY SUPPORT DEVICE TYPE (NATIONAL NEONATAL DATA SET) for the first day • Mechanical ventilation defined as 1 Endotracheal tube • No ventilation defined as any other answer
Infant: Inotropes administered on the first day	Data extracted from INOTROPE INFUSION RECEIVED INDICATOR for the first day • Dichotomous: Y/N Or DAILY CARE MEDICATION on day 1 only • 500098 Dopamine • 500096 Dobutamine • 500056 Adrenaline • 500210 Noradrenaline • 500116 Hydrocortisone • 1010173 Milrinone
Infant: Sepsis suspected on the first day	Data extracted from DAILY CARE INFECTIONS SEPSIS SUSPECTED INDICATOR for the first day • Y/N
Infant: Transfer on the first day	Data extracted from Admission Details SITE CODE (OF ADMITTING NEONATAL UNIT) or ORGANISATION CODE (OF ADMITTING NEONATAL UNIT) is different from Baby Demographics SITE CODE (OF ACTUAL PLACE OF DELIVERY) or ORGANISATION CODE (OF ACTUAL PLACE OF DELIVERY) And Baby Demographics EPISODE NUMBER is >1
Level of the initial neonatal unit	Data extracted from SITE CODE (OF ACTUAL PLACE OF DELIVERY)
Neonatal network	Data extracted from SITE CODE (OF ACTUAL PLACE OF DELIVERY)
Enteral feeding	Data extracted from DAILY CARE FLUIDS AND FEEDING ENTERAL FEED TYPE GIVEN on day 1 and 2 • Categorical: Only maternal milk feeding defined as any of 1 Breastfeeding, 2 Mothers fresh expressed breast milk, 3 Mothers frozen expressed breast milk on either day with no other code. • Categorical: Only donor milk feeding defined as 4 Donor expressed breast milk on either day with no other code.

Background variables for propensity score matching	
	• Categorical: Only formula defined as only 6 Formula milk on either day with no other code. • Categorical: Not feeding defined as 9 – Not applicable (nil by mouth) on both days with no other code. • Categorical: Mixed feeding as any combination of codes not consistent with the above categories.

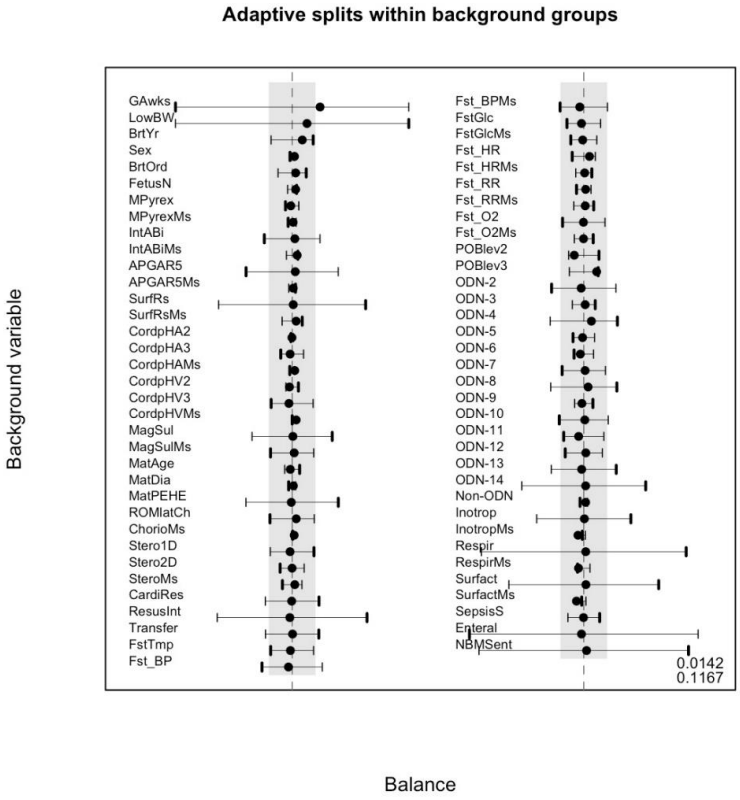
Outcomes	
Variable	**Data items**
Survival	Data extracted from DISCHARGE DESTINATION FROM NEONATAL CRITICAL CARE • Survival defined as any of 1, 2, 4, 5, 6 • Died defined as code 3, Died
Late-onset sepsis	NNAP definition Defined from Infection Cultures (Episodic) recorded after day 3 • Pure growth of pathogen from blood OR Pure growth of pathogen from CSF OR Either a pure growth of a skin commensal or a mixed growth with ≥3 clinical signs at the time of blood sampling
Necrotising enterocolitis	NNAP definition Defined from DISCHARGE DETAILS based on WAS NEC DIAGNOSED THIS ADMISSION answer Y With at least one clinical feature from: • Bilious gastric aspirate or emesis/Abdominal distension/Occult or gross blood in stool (no fissure) And at least one radiographic feature from: • Pneumatosis/Hepato-biliary gas/Pneumoperitoneum Where NNAP definition not recorded (e.g. prior to 2016): EITHER 1. Treatment for necrotising enterocolitis defined from Daily Care Gastrointestinal at any point during the neonatal unit stay: • Any entry (1 or 2) for TREATMENT TYPE FOR NECROTISING ENTEROCOLITIS OR 2. Any of the following diagnostic codes: • 1010683 Necrotising enterocolitis – suspected • 10708 Necrotising enterocolitis – Perforated • 15809 Necrotizing enterocolitis In a baby who was recorded as being nil by mouth for 5 or more days defined from the Daily Care Fluids and Feeding for a continuous period of 5 days • No under ENTERAL FEED TYPE GIVEN • No entry under FORMULA MILK OR MILK FORTIFIER TYPE • No value OR 0 for TOTAL VOLUME OF MILK RECEIVED • No entry under ENTERAL FEEDING METHOD While also receiving 5 or more days of antibiotics over the same 5 days as the baby was nil by mouth: Defined as 5 consecutive days of any of the following Daily care medication • 1010155 Benzyl Penicillin • 1010158 Augmentin • 1010179 Flucloxicillin

Outcomes	
	• 500012 Flucloxacillin • 500016 Gentamicin • 500072 Co-amoxiclav • 500086 Co-amoxiclav • 500084 Ciprofloxacin • 500029 Netilmicin • 500002 Amikacin • 500211 Tazocin • 500023 Metronidazole • 500040 Vancomycin • 500007 Cefotaxime • 500004 Ampicillin • 500009 Cefuroxime • 500008 Ceftazidime • 500175 Ceftriaxone • 500032 Piperacillin • 500206 Oflacillin • 500005 Azlocillin • 1010171 Linezolid • 1010271 Cefalexin • 1010139 Amoxicillin • 500070 Amoxicillin • 500128 Meropenem • 500118 Imepenem • 500145 Imipenem
Brain injury on imaging	Data extracted from CRANIAL ULTRASOUND SCANS (EPISODIC) Brain injury defined as: • INTRAVENTRICULAR HAEMORRHAGE GRADE (RIGHT SIDE) or INTRAVENTRICULAR HAEMORRHAGE GRADE (LEFT SIDE) code 3 or 4 (Grade 3/4 intraventricular haemorrhage) Or: • CYSTIC PERIVENTRICULAR LEUKOMALACIA OBSERVED DURING CRANIAL ULTRASOUND SCAN INDICATOR answer Y
Retinopathy of prematurity	Data extracted from RETINOPATHY OF PREMATURITY SCREENING (EPISODIC) Retinopathy of prematurity defined as: • RETINOPATHY OF PREMATURITY STAGE (LEFT EYE) or RETINOPATHY OF PREMATURITY STAGE (RIGHT EYE) any code except 0 (None seen)
Bronchopulmonary dysplasia	NNAP definition Significant bronchopulmonary dysplasia defined as: • DAILY SUMMARY at 36^{+0} receiving any respiratory support
Need for surgical procedures	Data extracted from PROCEDURE (OPCS ON NEONATAL CRITICAL CARE DAILY CARE DATE) Surgery defined as any of the following codes: • 100033 Surgery for meconium ileus (von) • 100076 Skin or soft tissue surgery requiring general or spinal anesthesia (Description Required • 11222 Closure of small intestine/ileal perforation • 11501 Laparoscopy • 11904 Colostomy • 11905 Ileostomy • 1010826 Major surgery Or:

Outcomes	
	• Daily item ANY MAJOR SURGERY TODAY answer Y
Seizures	Seizure defined as: SEIZURE OCCURRED INDICATOR • Y Or: DIAGNOSIS (ICD RECORDED ON DISCHARGE FROM NEONATAL CRITICAL CARE) with code • 10957 Seizures • 15192 Seizure disorder • 15194 Seizure disorder (cause unknown) • 15195 Status epilepticus • 15848 Seizures
Weight	Data extracted from Daily Care General Information PERSON WEIGHT IN GRAMS from the final day
Head circumference	Data extracted from Daily Care General Information HEAD CIRCUMFERENCE IN CENTIMETRES from the final day

Long Term Outcomes	
Variable	**Data items**
Blindness	Defined as an answer of Yes to the question “Does this child have a visual impairment?” on the NNAP form
Deafness	Defined as an answer of Yes to the question “Does this child have a hearing impairment?” on the NNAP form
Ability to walk	Defined as an answer of Yes to the question “Is this child unable to walk without assistance?” on the NNAP form

eFigure 1: Balance plot for all background variables



Balance plot illustrating balance before and after matching in the comparative study.

Each background variable is illustrated by one plot with two arms, and comparison is between neonates given PN in the first postnatal week and those not given PN. The ends of the arms illustrate the difference between cohorts before matching (the thick arm indicates the direction of the difference, this is then mirrored in the thin end to illustrate the magnitude of the imbalance). The plot illustrates the difference after matching.

The shaded grey area indicates one standard deviation (for each variable).

Standardised mean difference reported in lower right corner (upper value is after matching, lower value is before matching). Values of less than 0.1 are considered to illustrate a good match.

Abbreviations:

For all categories the suffix –Ms denotes missing data.

Gawks: Gestational age in weeks. LowBW: Low birth weight. BrtYr: Birth year. BrtOrd: Birth order. FetusN: Fetus number. MPyrex: Maternal pyrexia in labor. IntABi: Neonate intubated during resuscitation. APGAR5: 5 minute Apgar score. SurfRs: Surfactant administered during resuscitation. CordpHA2: Arterial Cord pH≤7.29. CordpHA3: Arterial cord pH≥7.30. CordpHV2: Venous cord pH

≤7.29. CordpHV3: Venous cord pH≥7.30. MagSul: Antenatal magnesium sulfate administered. MatAge: Maternal age. MatDia: Maternal diabetes mellitus. MatPEHE: Maternal pre-eclampsia or gestational hypertension. ROMMatCh: Prolonged prelabour rupture of membranes or maternal chorioamnionitis. Stero1D: Incomplete course of antenatal steroids. Stero2D: complete course of antenatal steroids. CardiRes: Chest compressions during neonatal resuscitation. Transfer: Transfer of the neonate on the first postnatal day. FstTmp: First temperature reading after neonatal unit admission. Fst_BP: First mean blood pressure reading after neonatal unit admission. FstGlc: First blood glucose reading after admission to neonatal unit. Fst_HR: First heart rate reading after admission to neonatal unit. Fst_RR: First respiratory rate reading after admission to neonatal unit. Fst_O2: First oxygen saturation reading after admission to neonatal unit. POBlev2: Neonate first admitted to a level 2 neonatal unit. POBlev3: Neonate first admitted to a level 3 neonatal unit. ODN: Different neonatal network to which neonate was first admitted. Non-ODN: Neonate first admitted to a neonatal unit not part of a neonatal network. Inotrop: Neonate received inotropes after admission to neonatal unit on first postnatal day. Respir: Neonate mechanically ventilated after admission to neonatal unit on first postnatal day. Surfact: Neonate received surfactant after admission to neonatal unit on first postnatal day. SepsisS: Neonate treated for suspected sepsis after admission to neonatal unit on first postnatal day. Enteral: Neonate given milk feeds after admission to neonatal unit on first postnatal day. NBM: Neonate not given milk feeds after admission to neonatal unit on first postnatal day.

eTable 4: Full background characteristics for neonates

	Entire cohort				Matched cohort			
	No PN group (N=19,080)		PN group (N=16,282)		No PN group (N=8,146)		PN group (N=8,146)	
		Missing data		Missing data		Missing data		Missing data
Gestational age (weeks), mean (SD)	31.5 (0.7)	0	30.9 (0.8)	0	31.2 (0.8)	0	31.2 (0.8)	0
Birthweight (kg), mean (SD)	1.74 (0.28)	6	1.47 (0.32)	5	1.67 (0.28)	0	1.59 (0.29)	0
Birthweight Z score, mean (SD)	0.12 (0.95)	6	-0.16 (1.0)	5	0.01 (0.91)	0	-0.05 (0.88)	0
Proportion small for gestational age, n (%)	834 (4.4)	6	3773 (23.2)	5	710 (8.7)	0	715 (8.8)	0
Infant sex, n (%)								
Male	10293 (53.9)	0	8858 (54.4)	0	4482 (55.0)	0	4413 (54.2)	0
Female	8787 (46.1)	0	7424 (45.6)	0	3664 (45.0)	0	3733 (45.8)	0
Year of birth, mean (SD)	2014.4 (1.7)	0	2014.6 (1.7)	0	2014.5 (1.7)	0	2014.5 (1.7)	0
Maternal factors								
Maternal age, mean (SD)	30.5 (6.3)	158	30.7 (6.3)	122	30.8 (6.3)	67	30.8 (6.2)	61
Maternal complications of pregnancy[a], n (%)	14025 (73.5)	0	12234 (75.1)	0	6055 (74.3)	0	5177 (75.8)	0
Maternal medical problems, n (%)	10936 (57.3)	0	9805 (60.2)	0	4763 (58.5)	0	4822 (59.2)	0
Antenatal steroids, n (%)								
Yes, complete course	3312 (18.2)	922	2515 (16.1)	647	1328 (17.0)	350	1324 (17.0)	339
Yes, incomplete course	12891 (71.0)	922	11701 (74.8)	647	5678 (72.8)	350	5694 (72.9)	339
No	1955 (10.8)	922	1419 (9.1)	647	790 (10.1)	350	789 (10.1)	339
Magnesium sulphate, n (%)	1554 (17.8)	10345	2183 (26.6)	8075	846 (21.6)	4234	866 (22.1)	4224

	Entire cohort				Matched cohort			
	No PN group (N=19,080)		PN group (N=16,282)		No PN group (N=8,146)		PN group (N=8,146)	
		Missing data		Missing data		Missing data		Missing data
Infant factors after birth								
Umbilical arterial pH, mean (SD)	7.3 (0.1)	11297	7.3 (0.1)	9559	7.3 (0.1)	4743	7.3 (0.1)	4716
Umbilical venous pH, mean (SD)	7.3 (0.1)	11146	7.3 (0.1)	9512	7.3 (0.1)	4684	7.3 (0.1)	4674
Apgar score at 5 minutes, median (IQR)	9 (8-10)	1628	9 (8-9)	1455	9 (8-10)	731	9 (8-10)	696
Intubation during resuscitation, n (%)	1730 (9.1)	0	3275 (20.1)	0	1175 (14.4)	0	1180 (14.5)	0
Surfactant during resuscitation, n (%)	1886 (10.9)	1764	3419 (23.5)	1714	1271 (17.2)	740	1269 (17.2)	763
Cardiac compressions during resuscitation, n (%)	272 (1.4)	0	446 (2.7)	0	169 (2.1)	0	191 (2.3)	0
Drugs during resuscitation, n (%)	214 (1.1)	0	320 (2.0)	0	136 (1.7)	0	119 (1.5)	0
Infant factors on first day								
Admission temperature, mean (SD)	36.7 (0.6)	112	36.7 (0.6)	85	36.8 (0.6)	42	36.8 (0.6)	45
Admission heart rate, mean (SD)	156 (18.0)	1208	157 (18.2)	1171	157 (18.0)	525	157 (18.1)	526
Admission blood pressure, mean (SD)	39.5 (10.5)	4479	38.4 (11.0)	3143	39.0 (11.2)	1665	39.0 (11.8)	1631
Admission respiratory rate, mean (SD)	53.6 (39.2)	1930	52.4 (13.7)	1861	53.4 (57.8)	846	52.8 (13.5)	840
Admission oxygen saturation, mean (SD)	93.4 (7.8)	1286	93.6 (7.6)	1268	93.3 (7.8)	573	93.3 (7.8)	563

	Entire cohort				Matched cohort			
	No PN group (N=19,080)		PN group (N=16,282)		No PN group (N=8,146)		PN group (N=8,146)	
		Missing data		Missing data		Missing data		Missing data
Admission blood sugar, mean (SD)	3.1 (1.9)	3843	2.8 (4.3)	2923	3.0 (3.9)	1486	3.0 (5.7)	1503
Surfactant administered on NNU on first day, n (%)	1854 (9.9)	290	3422 (21.3)	230	1263 (15.7)	77	1296 (16.1)	77
Ventilated on first day, n (%)	2833 (14.9)	108	5364 (33.1)	62	1932 (23.8)	38	1979 (24.4)	39
Inotropes on first day, n (%)	186 (1.0)	298	658 (4.1)	242	128 (1.6)	82	149 (1.8)	75
Treated for sepsis on first day, n (%)	8487 (44.5)	0	7795 (47.9)	0	3837 (47.1)	0	3843 (47.2)	6237
Enteral feeding on first day, n (%)	14401 (75.5)	0	8593 (52.8)	0	4570 (56.1)	0	4555 (55.9)	0
Organisational factors								
Level of neonatal unit, n (%)								
Level 1 (SCBU)	2578 (13.5)	1	1197 (7.4)	1	745 (9.1)	1	686 (8.4)	1
Level 2 (LNU)	8313 (43.6)	1	7621 (46.8)	1	3773 (46.3)	1	3883 (47.7)	1
Level 3 (NICU)	7963 (41.7)	1	7294 (44.8)	1	3525 (43.3)	1	3463 (42.5)	1
Transferred on first day, n (%)	810 (4.2)	0	1112 (6.8)	0	450 (5.5)	0	464 (5.7)	0

eTable 5: Sensitivity analysis for hidden bias due to unobserved background variable

Γ	P value for difference in outcome between groups				
	Survival	Bronchopulmonary dysplasia	Late-onset sepsis	Necrotising enterocolitis	Need for surgery
1.0	0.00	0.00	0.00	0.00	0.00
1.2	0.00	0.00	0.00	0.00	0.00
1.4	0.04	0.00	0.00	0.00	0.01
1.6	0.28	0.00	0.00	0.00	0.12
1.8	0.83	0.05	0.00	0.00	0.45
2.0	N/A	0.66	0.01	0.09	0.95
2.2	N/A	N/A	0.07	0.70	N/A
2.4	N/A	N/A	0.22	N/A	N/A
2.6	N/A	N/A	0.48	N/A	N/A
2.8	N/A	N/A	0.80	N/A	N/A
3.0	N/A	N/A	N/A	N/A	N/A

Table contains P value seen for each outcome as Γ changes for hypothetical missing variable. Γ is increased and the effect on the P value calculated. The critical value of Γ that would overturn the results that we found are as follows for each outcome: Survival Γ=1.6; Bronchopulmonary dysplasia Γ=1.8; Late-onset sepsis Γ=2.2; Necrotising enterocolitis Γ =2.0 and Need for surgery Γ=1.6

eTable 6: Magnitude of imbalance seen in observed background variables in unmatched cohort

Γ	Variable
6.61	Small for gestational age
4.28	Inotropes on first day
4.21	Neonatal network
3.46	Gestational age at birth
2.82	Mechanical ventilation on the first day
2.76	Enteral feeding
2.53	Intubated at resuscitation
2.47	Surfactant administered on the first day
2.42	Surfactant administered during resuscitation
1.94	Chest compressions administered during resuscitation
1.78	Maternal severe pre-eclampsia
1.75	Maternal receipt of magnesium sulphate
1.65	Transferred on first day
1.51	Apgar score at 5 minutes

Γ gives a measure of imbalance seen in observed variables in the unmatched cohort. It can be compared to the values of Γ calculated in the sensitivity analysis to give an indication of the plausibility of an unobserved variable existing with sufficient imbalance to account for the observed results.

Variables listed are those with Γ>1.4, listed by the magnitude of Γ

All variables treated as dichotomous variables. Continuous variables have been divided to create a dichotomous variable. For categorical variables, each category was treated as a Yes/No dichotomous variable, and the largest value of Γ is presented.

eTable 7: Post-hoc analysis of death or each major morbidity

	Matched cohort					
	No PN group (N=8,146)		PN group (N=8,146)		Treatment effect (95% confidence interval)	P value
		Missing data		Missing data		
Death or brain injury on imaging, n (%)	228 (2.8)	0 [b]	151 (1.9)	0 [b]	-0.94 (-1.39, -0.48)	<.001 [a]
Death or bronchopulmonary dysplasia, n (%)	458 (5.8)	198	682 (8.5)	106	2.7 (1.9, 3.5)	<.001 [a]
Death or late onset sepsis, n (%)	234 (2.9)	0 [b]	244 (3.0)	0 [b]	0.13 (-0.38, 0.64)	0.62
Death or necrotising enterocolitis, n (%)	456 (5.6)	0 [b]	711 (8.7)	0 [b]	3.1 (2.4, 3.9)	<.001 [a]
Death or need for surgical procedures, n (%)	240 (3.0)	0 [b]	215 (2.6)	0 [b]	-0.31 (-0.81, 0.19)	0.21
Death or retinopathy of prematurity, n (%)	293 (5.7)	3007	254 (4.6)	2642	-1.1 (-1.7,-0.41)	0.001 [a]
Death or seizures, n (%)	228 (2.8)	3	182 (2.1)	8	-0.63 (-1.1, -0.16)	0.007 [a]

[a] indicates a statistically significant result (p<0.05).
Outcomes corrected for multiple comparisons using Bonferroni-Holm method.
[b] amount of missing data uncertain as absence of data interpreted as absence of outcome

eTable 8: United Kingdom Neonatal Collaborative leads at contributing neonatal units

Institution	Lead
England	
Airedale General Hospital	Dr Matthew Babirecki
Arrowe Park Hospital	Dr Anand Kamalanathan
Barnet Hospital	Dr Tim Wickham
Barnsley District General Hospital	Dr Kavi Aucharaz
Basildon Hospital	Dr Aashish Gupta
Basingstoke & North Hampshire Hospital	Dr Nicola Paul
Bassetlaw District General Hospital	Dr L M Wong
Bedford Hospital	Dr Anita Mittal
Birmingham City Hospital	Dr Lindsay Halpern
Birmingham Heartlands Hospital	Dr Pinki Surana
Birmingham Women's Hospital	Dr Matt Nash
Bradford Royal Infirmary	Dr Sunita Seal
Broomfield Hospital, Chelmsford	Dr Ahmed Hassan
Calderdale Royal Hospital	Dr Karin Schwarz
Chelsea & Westminster Hospital	Dr Shu-Ling Chuang
Chesterfield & North Derbyshire Royal Hospital	Dr Aiwyne Foo
Colchester General Hospital	Dr Jo Anderson
Conquest Hospital	Dr Graham Whincup
Countess of Chester Hospital	Dr Stephen Brearey
Croydon University Hospital	Dr Morris
Croydon University Hospital	Dr Srirambhatla
Cumberland Infirmary	Dr Yee Aung
Darent Valley Hospital	Dr Abdul Hasib
Darlington Memorial Hospital	Dr Mehdi Garbash
Derriford Hospital	Dr Alex Allwood
Diana Princess of Wales Hospital	Dr Pauline Adiotomre
Doncaster Royal Infirmary	Dr Nigel Brooke
Dorset County Hospital	Dr Abby Deketelaere
East Surrey Hospital	Dr Abdul Khader
Epsom General Hospital	Dr Sonia Spathis
Frimley Park Hospital	Dr Sanghavi Rekha
Furness General Hospital	Dr Anas Olabi
George Eliot Hospital	Dr Mukta Jain
Gloucester Royal Hospital	Dr Jennifer Holman
Good Hope Hospital	Dr Pinki Surana
Great Western Hospital	Dr Stanley Zengeya
Guy's & St Thomas' Hospital	Dr Geraint Lee
Harrogate District Hospital	Dr Sobia Balal
Hereford County Hospital	Dr Cath Seagrave
Hillingdon Hospital	Dr Tristan Bate
Hinchingbrooke Hospital	Dr Hilary Dixon
Homerton Hospital	Dr Narendra Aladangady
Hull Royal infirmary	Dr Hassan Gaili
Ipswich Hospital	Dr Matthew James
James Cook University Hospital	Dr M Lal
James Paget Hospital	Dr Ambadkar
Kettering General Hospital	Dr Poornima Pandey
Kings College Hospital	Dr Ravindra Bhat
King's Mill Hospital	Dr Simon Rhodes
Kingston Hospital	Dr Jonathan Filkin
Lancashire Women and Newborn Centre	Dr Savi Sivashankar
Leeds Neonatal Service	Dr Lawrence Miall
Leicester General Hospital	Dr Jonathan Cusack
Leicester Royal Infirmary	Dr Venkatesh Kairamkonda
Leighton Hospital	Dr Michael Grosdenier
Lincoln County Hospital	Dr Ajay Reddy
Lister Hospital	Dr J Kefas
Liverpool Women's Hospital	Dr Christopher Dewhurst

Luton & Dunstable Hospital	Dr Jennifer Birch
Macclesfield District General Hospital	Dr Gail Whitehead
Manor Hospital	Dr Krishnamurthy
Medway Maritime Hospital	Dr Ghada Ramadan
Milton Keynes General Hospital	Dr I Misra
Musgrove Park Hospital	Dr Chris Knight
New Cross Hospital	Dr Matt Nash
Newham General Hospital	Dr Imdad Ali
Nobles Hospital	Dr Prakash Thiagarajan
Norfolk & Norwich University Hospital	Dr Muthukumar
North Devon District Hospital	Dr Michael Selter
North Manchester General Hospital	Dr Ajit Mahaveer
North Middlesex University Hospital	Dr Neeraj Jain
Northampton General Hospital	Dr Subodh Gupta
Northumbria Specialist Emergency Care Hospital	Laura Winder
Northwick Park Hospital	Dr Richard Nicholl
Nottingham City Hospital	Dr Steven Wardle
Nottingham University Hospital (QMC)	Dr Steven Wardle
Ormskirk District General Hospital	Dr Andreea Bontea
Oxford University Hospitals, John Radcliffe Hospital	Dr Eleri Adams
Peterborough City Hospital	Dr Katharine McDevitt
Pilgrim Hospital	Dr Ajay Reddy
Pinderfields General Hospital (Pontefract General Infirmary)	Dr David Gibson
Poole General Hospital	Prof Minesh Khashu
Princess Alexandra Hospital	Dr Chinnappa Reddy
Princess Anne Hospital	Dr Mark Johnson
Princess Royal Hospital	Dr P Amess
Princess Royal Hospital (previously Royal Shrewsbury Hospital)	Dr Deshpande
Princess Royal University Hospital	Dr Elizabeth Sleight
Queen Alexandra Hospital	Dr Charlotte Groves
Queen Charlotte's Hospital	Dr Lidia Tyszcuzk
Queen Elizabeth Hospital, Gateshead	Dr Anne Dale
Queen Elizabeth Hospital, King's Lynn	Dr Glynis Rewitzky
Queen Elizabeth Hospital, Woolwich - see notes	Dr Olutoyin Banjoko
Queen Elizabeth the Queen Mother Hospital	Dr Bushra Abdul-Malik
Queen's Hospital, Burton on Trent	Dr Dominic Muogbo
Queen's Hospital, Romford	Dr Khalid Mannan
Queen's Hospital, Romford 2	Dr Khalid Mannan
Rosie Maternity Hospital, Addenbrookes	Dr Angela D'Amore
Rotherham District General Hospital	Dr Soma Sengupta
Royal Albert Edward Infirmary	Dr Christos Zipitis
Royal Berkshire Hospital	Dr Peter De Halpert
Royal Bolton Hospital	Dr Paul Settle
Royal Cornwall Hospital	Dr Paul Munyard
Royal Derby Hospital	Dr John McIntyre
Royal Devon & Exeter Hospital	Dr Chrissie Oliver
Royal Hampshire County Hospital	Dr Lucinda Winckworth
Royal Lancaster Infirmary	Dr Joanne Fedee
Royal Oldham Hospital	Dr Natasha Maddock
Royal Preston Hospital	Dr Richa Gupta
Royal Stoke University Hospital	Dr Jyoti Kapur
Royal Surrey County Hospital	Dr Ben Obi
Royal Sussex County Hospital	Dr P Amess
Royal United Hospital	Dr Stephen Jones
Royal Victoria Infirmary	Dr Naveen Athiraman

Russells Hall Hospital	Dr Chandan Gupta
Salisbury District Hospital	Dr Jim Baird
Scarborough General Hospital	Dr Kirsten Mack
Scunthorpe General Hospital	Dr Pauline Adiotomre
Southend Hospital	Dr Vineet Gupta
Southmead Hospital	Dr Faith Emery
St George's Hospital	Dr Charlotte Huddy
St Helier Hospital	Dr Ralf Hartung
St Mary's Hospital, IOW	Dr Akinsola Ogundiya
St Mary's Hospital, London	Dr Lidia Tyszcuzk
St Mary's Hospital, Manchester	Dr Ngozi Edi-Osagie
St Michael's Hospital	Dr Pamela Cairns
St Peter's Hospital	Dr Peter Martin
St Richard's Hospital	Dr Nick Brennan
Stepping Hill Hospital	Dr Carrie Heal
Stoke Mandeville Hospital	Dr Sanjay Salgia
Sunderland Royal Hospital	Dr Majd Abu-Harb
Tameside General Hospital	Dr Jacqeline Birch
The Jessop Wing, Sheffield	Dr Porus Bastani
The Royal Free Hospital	Dr Marice Theron
The Royal London Hospital - Constance Green	Dr Vadivelam Murthy
Torbay Hospital	Dr Siba Paul
Tunbridge Wells Hospital	Dr Hamudi Kisat
University College Hospital	Dr Giles Kendall
University Hospital Coventry	Dr Puneet Nath
University Hospital Lewisham	Dr Ozioma Obi
University Hospital of North Durham	Dr Mehdi Garbash
University Hospital of North Tees	Dr Hari Kumar
Victoria Hospital, Blackpool	Dr Chris Rawlingson
Warrington Hospital	Dr Delyth Webb
Warwick Hospital	Dr Bird
Watford General Hospital	Dr Sankara Narayanan
West Cumberland Hospital	no lead
West Middlesex University Hospital	Dr Eleanor Hulse
West Suffolk Hospital	Dr Ian Evans
Wexham Park Hospital	Dr Sanjay Jaisal
Whipps Cross University Hospital	Dr Caroline Sullivan
Whiston Hospital	Dr Ros Garr
Whittington Hospital	Dr Wynne Leith
William Harvey Hospital	Dr Vimal Vasu
Worcestershire Royal Hospital	Dr Liza Harry
Worthing Hospital	Dr Katia Vamvakiti
Wythenshawe Hospital	Dr Ngozi Edi-Osagie
Yeovil District Hospital	Dr Megan Eaton
York District Hospital	Dr Sundeep Sandhu
Wales	
Singleton Hospital	Dr Arun Ramachandran
Glan Clwyd Hospital	Dr Ian Barnard
Glangwili General Hospital	Dr Prem Pitchaikani
The Grange University Hospital	Dr Sunil Reddy
Prince Charles Hospital	Dr Iyad Al-Muzaffar
Princess of Wales Hospital	Dr Kate Creese
University Hospital of Wales	Dr Nitin Goel
Withybush Hospital	Dr Vishwa Narayan
Wrexham Maelor Hospital	Dr Brendan Harrington
Ysbyty Gwynedd	Dr Mike Cronin