Statistical analysis plan

Study title	Optimising kangaroo care to reduce neonatal severe infection/sepsis and resistant bacterial colonisation among high-risk infants in neonatal intensive care: a pragmatic, multicentre, parallel cluster randomised hybrid implementation-effectiveness study
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Authorised by:

Name:	Dr. Julia Bielicki [MD, MPH, PhD]
Role:	Chief Investigator
Name:	Dr. Elske Sieswerda [MD, PhD]
Role:	Senior scientific co-ordinator
Name:	Laura Mangiarini
Role:	Sponsor Representative
Name:	Dr. C. Henri van Werkhoven [MD, PhD]
Role:	Statistician

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Sponsor:

Signature

Firmato da:
Laura Mangiarini
Nome firmatario: Laura Mangiarini
Motivo per la firma: Approvo il documento
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0F5FD31B122640C7A5AB4A3E74F51EAC

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Date of Signature
(dd/mmm/yyyy)

Name: Laura Mangiarini
Title: Chief Program Officer
Institution: Fondazione Penta ETS (Penta)
Address: Corso Stati Uniti 4, 35127 Padova, Italy

Chief Investigator:

Signature

Signed by:
Julia Bielicki
Signer Name: Julia Bielicki
Signing Reason: I approve this document
Signing Time: 02 March 2026 | 08:20 CET
308F8D3D504749F1BFE41F84942F18D5

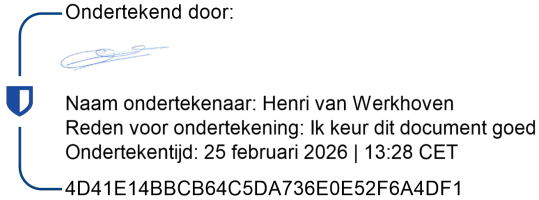
02 March 2026 | 08:20 CET

Date of Signature
(dd/mmm/yyyy)

Name: Julia Bielicki [MD, MPH, PhD]
Title: Reader in Paediatric Infectious Diseases St George's,
Institution: St George's, University of London
Address: Cranmer Terrace, SW17 0RE, London, United Kingdom

Statistician:

Signature



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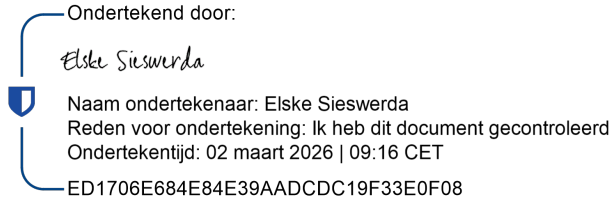
Date of Signature
(dd/mmm/yyyy)

Name	Henri van Werkhoven [MD, PhD]
Title	Assistant professor in Clinical Epidemiology
Institution	Julius Center for Health Sciences and Primary Care
Address	University Medical Center Utrecht, P.O. Box 85500

Senior Scientific Coordinator:

Signature



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Date of Signature
(dd/mmm/yyyy)

Name	Elske Sieswerda [MD, PhD]
Title	Clinical microbiologist and epidemiologist
Institution	Julius Center for Health Sciences and Primary Care
Address	University Medical Center Utrecht, P.O. Box 85500

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1 ABBREVIATIONS AND STUDY DEFINITIONS

1.1 ABBREVIATIONS

ABBREVIATION	EXPANSION
BPD	Bronchopulmonary Dysplasia
CPN	Clinical Practice Network
CSF	Cerebrospinal Fluid
DAI	Device-associated Infection
DSMB	Data Safety Monitoring Board
IVH	Intraventricular Haemorrhage
IDMC	Independent Data Monitoring Committee
IPC	Infection, Prevention and Control
KC	Kangaroo Care
LOCF	Last observation carried forward
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
PCR	Polymerase Chain Reaction
PPS	Point Prevalence Survey
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
SAP	Statistical Analysis Plan
StSC	Skin-to-Skin Contact
SSI	Surgical Site Infection
VAP	Ventilator-associated pneumonia

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned statistical analyses to address effectiveness objectives and quantitative implementation objectives within the **NeoDeco** study "**Optimising kangaroo care to reduce neonatal severe infection/sepsis and resistant bacterial colonisation among high-risk infants in neonatal intensive care: a pragmatic, multicentre, parallel cluster randomised hybrid implementation-effectiveness study**".

The SAP should be reviewed at least annually, or as and when changes to the planned statistical analyses occur. When an updated version is created, it must be reviewed and approved by those listed on the cover page, and a reason for revision must be listed in the revision history table.

Related documents

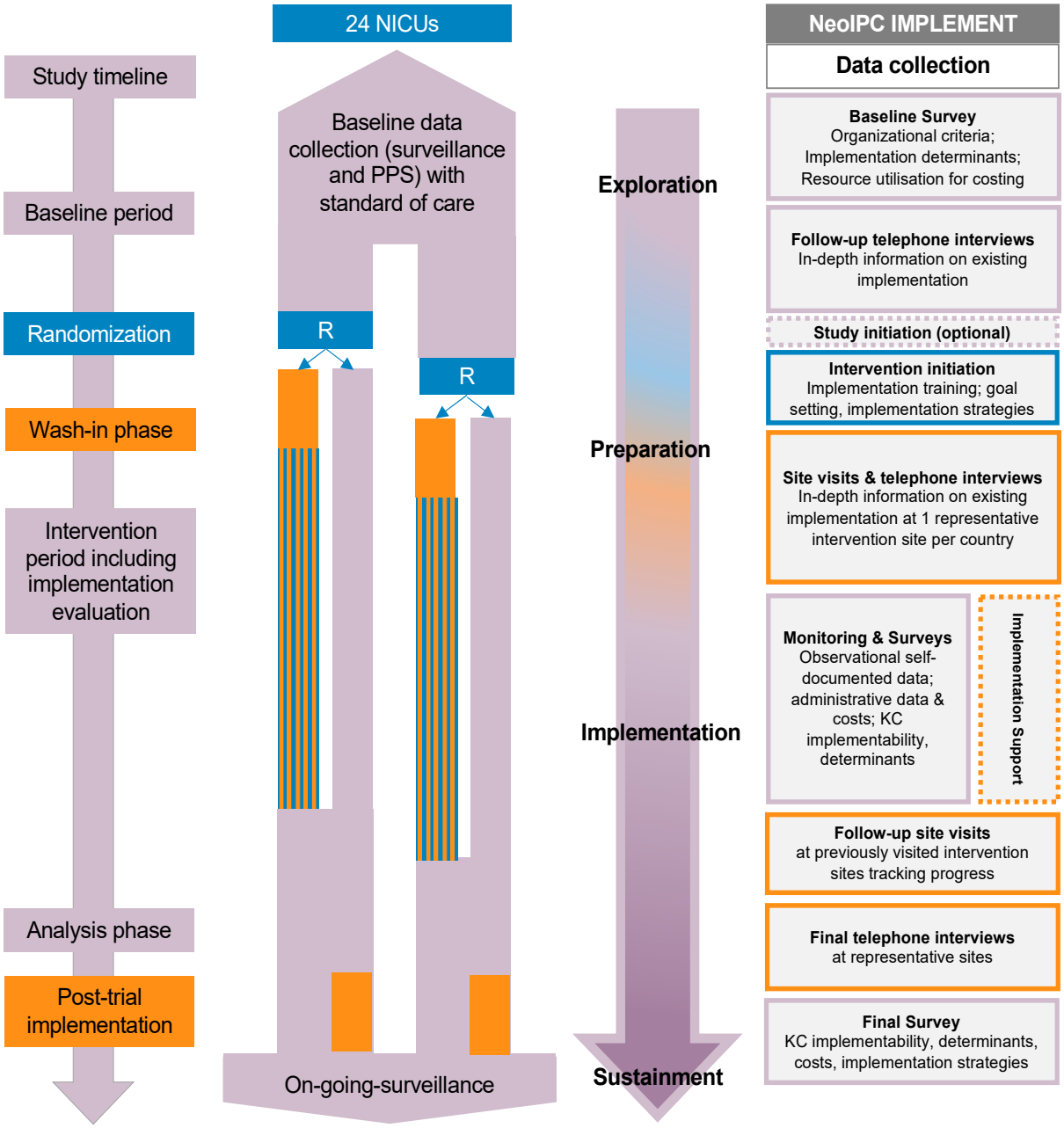
- NeoDeco study protocol version 4.0 (23-Dec-2024)
- NeoIPC surveillance manual version 1.2 (01 – Aug – 2023)
- NeoDeco Data Management Plan version 1.0 (01-Aug-2024)
- NeoDeco codebook version 2.0 (13-Mar- 2025)
- Restricted Randomization plan version 2.0 (27-Jan-2025)

3 STUDY METHODS

3.1 STUDY DESIGN

NeoDeco is a pragmatic, multicentre, international, parallel group, cluster randomised hybrid effectiveness-implementation study with baseline assessment, wash-in period and staggered randomisation. The study focuses on investigating the effectiveness (i.e. superiority) of implementing optimised kangaroo care (KC) for infection prevention and control outcomes (IPC), with standard delivery of KC without specific implementation support or strategies as the comparator of interest. KC, including regular skin-to-skin contact (StSC), is already part of standard care in all participating units. However, implementation is known to be suboptimal in the absence of specific implementation support. Neonatal units participating in NeoDeco will be randomised to receive implementation support during the study (intervention arm) or after the study completion (standard care arm). For a more extensive summary of the study design, see protocol synopsis. The study schema is illustrated in Figure 1.

Due to the nature of the intervention and the study design, blinding of parents or guardians, care providers and on-site research staff to the treatment allocation is not possible. Technicians performing PCRs and investigators performing the final analyses will be blinded to the allocated intervention.



Note: At each randomisation (R), a minimum of 10 NICUs are randomly allocated to the intervention (optimised KC) arm or the standard of care arm in a 1:1 manner. NICUs allocated to the control SOC arm will be given the opportunity for implementation of optimised KC in the post-trial period.

Figure 1: Graphic display of the proposed cluster randomised study design with staggered randomisation with two staggers.

3.2 DATA COLLECTION

NeoDeco has three data collection instruments: (1) NeoIPC Surveillance; (2) Point Prevalence Surveys (PPS), and (3) unit-level data collection.

NeoIPC Surveillance longitudinally collects data on hospital-acquired infections in high-risk infants in participating units. For most analyses using NeoIPC Surveillance data, only data from enrolled infants with informed consent are used. For the secondary analysis of the primary endpoint neonatal severe

infection/sepsis, cluster-aggregated data from NeoIPC Surveillance including all high-risk infants will be used (surveillance-based neonatal severe infection/sepsis).

PPS include weekly cross-sectional clinical data collection of enrolled infants and weekly (baseline period) or four-weekly (post-baseline period) stool sample collection to define resistant bacterial colonisation.

Unit-level data collection includes IPC and care practices at the unit and the total numbers of infant admissions according to risk status and the number of high-risk infants with major non-infection neonatal morbidity at the unit during study periods.

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Supplement Table 1 summarizes which endpoint is collected through which data collection tool. Data collection ends at discharge, transferal to another non-participating ward or another hospital, death, or withdrawal of consent.

4.1 BASELINE ASSESSMENT

To improve balance in important cluster characteristics between the study arms and increase power of the study, we will collect data during a baseline period preceding randomisation. Cluster-level data from the baseline period will be used for our randomisation procedure (chapter 3.4), sample size calculation (chapter 3.5) and statistical analyses of the study (chapter 6). Sample size calculations are based on a fixed baseline period duration of 3 months for all sites. In practice sites within one stagger may start their baseline period at different dates. For pragmatic reasons, a minimum baseline period of two months will be accepted.

4.2 RANDOMISATION

The unit of randomisation and implementation of the intervention is the neonatal unit (cluster). Each cluster will consist of one neonatal unit. We will perform cluster randomisation in two staggers according to a computer algorithm. The size and groupings of the staggers will be based on pragmatic reasons. In the third month of baseline data collection, the first stagger of neonatal units will be randomised 1:1 to the intervention or control arm. A subsequent stagger of neonatal units will be randomised using the same approach conditional on at least three months of baseline surveillance data collection and 1 month colonisation data. The minimum defined number of clusters per stagger is ten.

We will use restricted randomisation to reduce the risk of imbalance between the intervention and control neonatal units in cluster-level characteristics from the baseline period that are associated with the co-primary outcomes (baseline cluster-level neonatal severe infection/sepsis risk, cluster-level resistant colonisation pressure during the baseline period or in the colonisation assessment phase and baseline level of skin-to-skin care (StSC) use at the cluster level). In addition, to facilitate implementation evaluation and cost evaluation in each country, we will restrict randomisation options such that each country (Greece, Italy, Spain, Switzerland, United Kingdom) includes at least one intervention and one control neonatal unit.

Per stagger, an independent statistician will randomly select a randomisation sequence from all potential sequences that allow for balance between study arms in these key baseline cluster-level

characteristics while maintaining sufficient unpredictability and randomness. For technical details on the restricted randomisation procedure, we refer to the separate document on this topic.

4.3 SAMPLE SIZE CALCULATION

For the sample size calculation, we used the Stata command clustersampsi.[1] This command allows to incorporate clustering, a correlation between the cluster-level primary outcome in the baseline and intervention period, and variation in cluster size to calculate the sample size needed for a cluster randomized trial with baseline assessment.

Up to 24 neonatal units will be included and will contribute 2-3 months of data for the baseline period and up to 10 months for the intervention period. The estimated sample size for the intervention period is based on the primary outcome, i.e. the proportion of high-risk infants with at least one episode of neonatal severe infection/sepsis, from 72 hours after birth until neonatal unit discharge. This outcome has previously been used in large-scale neonatal infection prevention trials, allowing sound assumptions to be made to inform sample size calculation.[2]

In this study, 12 clusters (i.e., neonatal units) will be randomly allocated to the optimised KC intervention while 12 clusters are allocated to the standard care arm after a baseline period for 2-3 months. The intervention period will be up to 10 months after a wash-in period of 2 months, with data collection of up to 13 months in total (including the baseline period, excluding the wash-in period) and a planned total study duration of up to 15 months.

Conservatively assuming an average intervention period of 9 months, an average of 66 high-risk infant inclusions per cluster in the intervention period, a correlation of 0.60 between cluster-level neonatal severe infection/sepsis risk at baseline and intervention period, and an intra-cluster correlation coefficient of 0.01, we have 82% power to detect a 7.5% absolute reduction in neonatal severe infection/sepsis from 30% (without optimised KC) to 22.5% (with optimised KC), corresponding to a 25% relative reduction. For this calculation we assumed negligible loss to follow-up, a coefficient of variation for cluster size of 0.75, and a two-sided alpha=0.050. ICC was based on providing a reasonable range of expected cumulative incidences of neonatal severe infection/sepsis across clusters. We assumed a autocorrelation for the cluster-level cumulative incidence between baseline and intervention period of 0.6 as reasonable for a moderately stable outcome such as neonatal sepsis and with baseline and intervention data collected within 15 months.[3]

In total, 3080 high-risk infants are expected to be included at the participating units during baseline and intervention period (excluding wash-in period), with an estimated total of 1980 high-risk infants contributing data to the intervention period (excluding baseline and wash-in period).

4.4 FRAMEWORK

We will conduct all statistical analyses using a superiority hypothesis testing framework, thereby assessing whether successful implementation of early, repeated, and sustained StSC improves selected outcomes in high-risk infants as compared to standard care.

4.5 INTERIM ANALYSES

In our study, there are no planned interim analyses.

4.6 TIMING OF FINAL ANALYSES

Final statistical analyses are timed when data collection of all sites in both staggers is completed, and the database is locked.

4.7 TIMING OF OUTCOME ASSESSMENTS

Infant-level data from NeoIPC Surveillance is collected prospectively. Infant-level clinical and colonization data from PPS is collected cross-sectionally at weekly and four-weekly intervals (see 3.2). Unit-level data collection is done at the end of baseline and at the end of the study period.

The main analyses will include data collected during baseline and study period. Data collected post-baseline and pre-study period (wash-in period) may be used for exploratory analyses assessing trends in outcome data.

4.8 STATISTICAL SOFTWARE

Analyses will be performed in R (version 4.4.0 or higher). Used R packages will be listed in the study report.

4.9 REPORTING

This SAP was written in accordance with published recommendations.[4] Reporting of study conduct and summary of study data will be according to the Consolidated Standards of Reporting Trials (CONSORT) statement reporting guidelines, including the extension to cluster randomised trials.[5,6]

5 STATISTICAL PRINCIPLES

The primary determinant of interest is the allocated intervention (i.e. optimized KC versus standard of care). Intervention clusters and their individual infants will be compared to control clusters and their individual infants.

5.1 LEVELS OF STATISTICAL SIGNIFICANCE

We will present estimates with 95% confidence intervals (CIs). A two-sided p-value less than 0.05 will be considered evidence of an effect, i.e. the observed association is unlikely to have occurred by chance alone.

5.2 ANALYSIS POPULATIONS

There are two levels of analysis: the cluster level and the individual infant level. At the cluster level, the analysis population includes all neonatal units that participated in NeoDeco. At the infant level, the analysis population includes all infants whose parents or legal guardians provided written informed consent to data and/or sample collection for NeoDeco. For infant-level analyses, cluster-level summary measures are derived from consented infants only. For analyses of cluster-aggregated outcomes (surveillance-based neonatal severe infection/sepsis and major non-infection neonatal morbidity), summary measures are derived from all high-risk infants (born at gestational age <32 weeks) registered in NeoIPC Surveillance or admitted to participating neonatal units during the study period, regardless of individual consent status.

For most clinical endpoints, we aim to analyse outcomes at the individual level. Cluster-aggregated outcomes (surveillance-based neonatal severe infection/sepsis and major non-infection neonatal morbidity) will be analysed at the cluster-level. For primary and secondary outcomes analysed at the

individual level, we will additionally perform cluster-level analyses as sensitivity analyses, i.e. to check for robustness of the result of the analysis. In case there is no appropriate fit of individual-level models of other endpoints, these cluster-level analyses will replace the main analysis.

Data are analysed according to the relevant study period (baseline period or intervention period) and according to the allocated intervention during the study period, irrespective of StSC receipt (i.e. intention-to-treat principle). Infants already hospitalized at the start of a study period will be included in the study population for endpoints based on repeated events, but excluded for endpoints based on first events, to prevent immortal time bias. For included infants already hospitalized at the start of the baseline period, data from before baseline is completed retrospectively. For included infants already hospitalized at the start of the intervention period, data from before the intervention period is already prospectively collected as part of the wash-in period. Only data collected after the start of a relevant study period will be included in the analyses. As an example, in case an infant is already hospitalized and has a first neonatal severe infection/sepsis episode before the start of the intervention period and a second episode after the start of the intervention period, this infant will be excluded for the assessment of the *cumulative incidence* of neonatal severe infection sepsis risk, because the endpoint only assesses first events and has already been reached prior to the start of the intervention period, i.e. the infant is no longer "at risk". However, the infant and the second episode will be included for the *incidence rate* of neonatal severe infection/sepsis and assessed based on hospitalization days since start of the intervention period, since this endpoint allows for analysis of repeated events, i.e. the infant stays "at risk" for another event. For PPS-derived endpoints such as resistant bacterial colonization, observations are assigned to the study period in which the PPS was conducted. Cluster-aggregated data such as surveillance-based neonatal severe infection/sepsis and major non-infection neonatal morbidity are assigned to the study period in which the data was collected, regardless of timing of hospitalization of individual infants.

5.3 ADHERENCE AND PROTOCOL DEVIATIONS

StSC receipt is monitored during the study. In addition, the level of implementation is defined per intervention cluster. For individual infants, motivated protocol deviations for application of StSC are allowed, documented, and listed in a final study report. For clusters, deviations of the implementation plan are allowed to fit in with site processes and needs. Such motivated deviations are fully documented.

In the primary analyses, we will analyse outcomes irrespective of the amount of StSC an infant received or the level of optimized KC implementation at the unit (i.e. intention-to-treat principle). We will present summary statistics of individual and cluster-level StSC receipt in both study arms. See secondary endpoints for description of the analysis.

Implementation evaluation, including deviations of the implementation plan at the cluster level, will be assessed by a mixed method approach within an implementation science evaluation framework. These methods are out of the scope of this statistical analysis plan.

6 STUDY POPULATION

For eligibility criteria in NeoDeco, we refer to the NeoDeco study protocol. At the infant level there are no exclusion criteria except for absence of informed consent. Informed consent is obtained separately for data and sample collection.

6.1 CLUSTER AND INFANT FLOW

We will summarise the following data on the study cluster and infant flow:

Neonatal units (clusters)

- Number of clusters
    - Included (i.e. started baseline period)
    - Randomized
    - Withdrawn

Infants

- Number of infants during baseline period, overall and per cluster
    - Admitted to the neonatal unit during the study period (all infants and high-risk infants [estimated eligible population] based on unit-level data collection)
    - Enrolled (i.e. informed consent in place)
        - Of which admitted to the neonatal unit before the start of the baseline period
        - Of which still admitted to the neonatal unit at the end of the baseline period
- Number of infants during intervention period, overall, in the intervention and control arm and per cluster
    - Admitted to the neonatal unit during the study period (based on unit-level data collection)
        - Total number of infants (including non-high risk)
        - Total number of high-risk infants (estimated eligible population)
    - Enrolled high-risk infants
        - Total number of infants
        - Number of enrolled infants admitted to the neonatal unit before the start of the intervention period
        - Number of enrolled infants still admitted to the neonatal unit at the end of the intervention period
    - Contributing to data collection through NeoIPC surveillance
        - Total number of high-risk infants registered (regardless of consent status)
        - Total number of enrolled infants (with informed consent)
        - Number of enrolled infants admitted to the neonatal unit before the start of the intervention period
        - Number of enrolled infants still admitted to the neonatal unit at the end of the intervention period
        - Total infant-days after start of the intervention period (enrolled infants only)
    - Contributing to data collection through PPS
        - Number of infants contributing to data collection through at least 1 PPS clinical data collection (including StSC adherence)
        - Number of infants contributing to data collection through at least 1 PPS sample collection (including resistant bacterial colonisation)
        - Withdrawn from PPS clinical data and/or sample collection

We will provide a Consort flow diagram to visualise the flow of clusters and infants as recommended by the Consort 2010 statement: extension to cluster randomised trials.[6]

6.2 BASELINE CHARACTERISTICS

We will summarise cluster-level characteristics during the baseline period and baseline cluster-level and infant-level characteristics during the intervention period for the intervention and control arm. We will summarize categorical data using counts and percentages. For continuous data, we will present the mean, standard deviation (SD), and range when the data are normally distributed, and the median, interquartile range (IQR), and range when the data are skewed. We will not perform statistical tests for significance on baseline characteristics but discuss clinical relevance of any observed imbalances. Characteristics that are summarised are:

6.2.1 Cluster-level characteristics during the baseline period

- NICU country
- Cluster size
- Neonatal severe infection/sepsis risk
- Prevalence of resistant bacterial colonisation
- Level of StSC
- Minimum expected target duration of StSC (intervention clusters); would-be minimum expected target duration of StSC (control clusters if they would have been allocated to intervention)

6.2.2 Baseline characteristics during the intervention period

- NICU
- Sex
- Birthweight
- Gestational age at birth
- Singleton vs multiple
- Mode of delivery
- Born in or outside hospital
- Day of life admitted
- Day of life enrolled in study

7 ANALYSIS

7.1 OUTCOME DEFINITIONS AND DETAILS

7.1.1 Primary outcome

Neonatal severe infection/sepsis

Neonatal severe infection/sepsis includes any of three diagnoses: clinical sepsis, laboratory-confirmed bloodstream infection (LC-BSI) and pneumonia, as registered by sites in NeoIPC Surveillance. Sites will record all episodes of neonatal severe infection/sepsis occurring >72 hours after admission until the end of the study (discharge or death) in high-risk infants. For this primary outcome, only data from infants with informed consent in place are used (see 4.2).

The cumulative incidence of neonatal severe infection/sepsis is the number of infants with a first episode of neonatal severe infection/sepsis (numerator) divided by the total number of infants at risk at a site during a study period (denominator).

7.1.2 Secondary outcomes

Resistant bacterial colonisation

Resistant bacterial colonisation involves detection of one or more pre-specified bacterial resistance genes in a stool sample of an infant during a PPS.

Prevalence of resistant bacterial colonisation during a PPS is the number of infants colonized with a pre-specified bacterial resistance gene (numerator) divided by the total number of infants contributing a stool sample to the PPS at a site (denominator).

Additionally, we will assess separate prevalences of resistant colonisation of the three components of the resistant bacterial colonisation outcome:

- Extended-spectrum beta-lactamase
- Carbapenemase
- Vancomycin resistance in enterococci

Infection outcomes – cumulative incidence

We will assess the separate cumulative incidences of the three components of the primary outcome and necrotising enterocolitis (NEC):

- Clinical sepsis
- LC-BSI
- Pneumonia
- NEC

Infection outcomes – incidence rate:

We will also define incidence rates of:

- Neonatal severe infection/sepsis
- LC-BSI
- Clinical sepsis

Incidence rate is the number of infection episodes (numerator) divided by the total time the infant contributed to a study period (denominator), expressed in infant days. Multiple episodes per infant can be included.

Surveillance-based neonatal severe infection/sepsis:

Cumulative incidence of neonatal severe infection/sepsis based on cluster-aggregated NeoIPC Surveillance data. The numerator is the number of high-risk infants with at least one episode of neonatal severe infection/sepsis registered in NeoIPC Surveillance during a study period. The denominator is the total number of high-risk infants registered in NeoIPC Surveillance during the same period.

Major non-infection neonatal morbidity

Major non-infection neonatal morbidity includes medically or surgically treated retinopathy of prematurity (ROP), high-grade intraventricular haemorrhage (IVH), cystic periventricular leukomalacia

(PVL) and/or bronchopulmonary dysplasia (BPD) at 36 weeks' post-menstrual age, as collected in the unit-level data collection.

Cumulative incidence of major non-infection neonatal morbidity is the number of high-risk infants with a first diagnosis of any of the major morbidity items (numerator) divided by the total number of high-risk infants admitted at a site during a study period (denominator). It is collected aggregated at the cluster level, separately for the baseline and intervention period, and is therefore a unit-level endpoint.

Neonatal unit mortality

Sites will record deaths occurring >72 hours after admission and during neonatal unit stay in infants with informed consent in place.

Neonatal unit mortality is the number of infants that died during neonatal unit stay (numerator) divided by the total number of infants at risk at a site during a study period (denominator).

Neonatal unit length of stay

Neonatal unit length of stay is the total number of calendar days an infant was hospitalised on the neonatal unit during the study period, independent of whether these are accrued as part of a primary or re-admission.

Antibiotic treatment

Sites will record antibiotic receipt during admission until discharge in infants with informed consent in place through both NeoIPC Surveillance and clinical data collection in PPS.

Days on antibiotic treatment is the total number of calendar days an infant received one or more antibiotics (numerator) divided by the total number of calendar days the infant contributed to a study period (denominator).

StSC duration

Sites will record StSC duration in hours and minutes in the preceding 24 hours in all infants with informed consent in place and hospitalized at the day of a weekly PPS.

StSC target attainment

The minimum expected target duration of StSC is a site-specific total daily duration of StSC to be provided per infant per day.

The proportion of infants receiving the minimum expected target duration of StSC is the number of infants contributing to a site's PPS that received the local minimum expected target duration of StSC (numerator) divided by the total number of infants contributing to the same PPS (denominator).

7.1.3 Exploratory outcomes

Acquisition of resistant colonisation

Acquisition of resistant colonisation is defined as detection of one or more pre-specified bacterial resistance genes while all previous stool samples in the same infant were negative for the same resistance gene(s).

Specific infection syndromes

We will assess the separate cumulative incidences of laboratory confirmed bloodstream infection with a relevant multidrug resistant pathogen, surgical site infections (SSI, including superficial, deep or organ-space SSI) and device-associated infection (DAI), as registered by sites in NeoIPC Surveillance.

Relevant multidrug resistant pathogens include 3rd generation cephalosporin-resistant Enterobacterales, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* faecium, or carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa*, or *Acinetobacter baumannii*.

Antibiotic use per antibiotic substance group

Days on antibiotic substance group treatment is the total number of calendar days an infant received one or more antibiotics from a substance group (numerator) divided by the total number of calendar days the infant contributed to a study period (denominator).

Classification of antibiotic substance groups will be adopted from the NeoOBS study.[7] In this approach, the backbone antibiotics are classified based on the Essential Medicines List for Children (EMLc) AWaRe classification (Access, Watch, Reserve).[8] As in NeoOBS, the "Watch" category will be subdivided into Low, Medium, and High Watch based on WHO guideline inclusion and resistance potential. Also, we will not classify antibiotics typically used as combination therapy alongside the backbone therapy, e.g. aminoglycosides, glycopeptides, and metronidazole.

Breastfeeding or mother's milk intake

Breastfeeding or mother's milk intake is defined as exposure to mother's milk given by any method in the preceding 24 hours in infants contributing to PPS. The proportion of infants receiving breastfeeding or mother's milk is the number of infants that received any breastfeeding or mother's milk intake (numerator) divided by the total number of infants contributing to a PPS at a site (denominator).

Human milk intake

Sites will record human milk intake >72 hours after admission until discharge in infants with informed consent in place through NeoIPC Surveillance. A human milk day is a day on which the patient's enteral feeding exclusively consists of (own mother's or donor) breast milk, including fortified breast milk.

Human milk intake is the total number of human milk days (numerator) divided by the total days the infant contributed to a study period (denominator).

7.2 ANALYSIS METHODS

7.2.1 Descriptive analyses

Endpoints

Cluster-level and intervention group-level primary and secondary endpoints will be visualized as a function of time, including baseline, wash-in, and intervention period, separately for the intervention and control arm.

We will describe all study endpoints with appropriate summary statistics in the intervention versus control arm during the intervention period. Endpoints are summarized at the cluster level, infant level, or both, as appropriate. This includes a summary of StSC receipt at the individual and cluster level and

the proportion of infants receiving the minimum expected target duration of StSC in intervention clusters; For the control clusters we will describe their would-be minimum expected target duration of StSC if they would have been allocated to intervention.

To describe the clustering structure, we will estimate the intra-cluster correlation (ICC) based on the observed study data of the primary outcome of neonatal severe infection/sepsis in all clusters during the baseline period and in control clusters during the intervention period. We will also report the ICCs for secondary endpoints. ICCs will be estimated with the ICCbin package using the analysis of variance estimate.[9,10] We will report on the correlation coefficient of neonatal severe infection/sepsis between baseline and intervention period as recommended by Copas et al, to verify the assumptions used in our sample size calculation.[3]

Other descriptive analyses

We will additionally report summary statistics of data collected during the intervention period, including potential mediating variables:

- Days with central venous catheter
- Days with peripheral venous catheter
- Days with invasive ventilation
- Days with non-invasive ventilation
- Receipt of probiotics

We will not do a formal mediation analysis. Finally, we will describe surgical procedures that infants underwent during the study period, stratified by intervention arm:

- Number of procedures by type of procedure (categorized)
- Distribution of the number of procedures per infant
- Median day of life on which first procedure took place + inter-quartile range
- A surgical procedure at least 48 hours before a first endpoint

7.2.2 General approach

To analyse the effect of the study intervention on study endpoints, we will primarily use mixed effects regression models on infant-level data, with a random intercept for cluster to account for intra-cluster correlation. When appropriate, we will also include a correlation structure to take into account dependency of observations that happen close in time; in that case, the specific correlation structure will be selected based on the Akaike Information Criterion. To estimate the intervention effect, the two determinants of interest will be (1) the randomly allocated intervention and (2) time in months since start of the intervention period (being zero for control clusters, assuming a linear effect). Regression link functions will be selected based on the distributional properties of the endpoint of interest. To adjust for baseline cluster differences and account for the restricted randomisation, we will include cluster level covariates from the baseline period that were also used for the restricted randomisation procedure in an analysis of covariance (ANCOVA) approach.[11] These cluster-level covariates from the baseline period are: cumulative incidence of neonatal severe infection/sepsis, average proportion of resistant colonisation, average total duration of StSC receipt per day, country and cluster size. For specific endpoints we also include its cluster-level mean from the baseline as a

covariate. In addition, the models will include important infant-level characteristics present at admission where appropriate.

To take into account the low number of clusters, small-sample adjustment will be done using the Between-Within approximation of denominator degrees of freedom.[12,13] The result will be reported as effect estimate with 95% confidence interval for the two determinants of interest. To statistically test the general hypothesis that the study intervention affects the outcome of interest, we will perform a likelihood ratio test, comparing the full model with a model not including the two determinants of interest. We will also report the estimated intervention effect at 3, 6 and 9 months after the start of the intervention period using the joint estimates for the two determinants of interest; the confidence intervals for the joint estimates will be derived from the variance-covariance matrix.

For endpoints with repeated cross-sectional assessment from PPS during the intervention period (resistant bacterial colonization, receipt of StSC, receipt of breastfeeding or mother's milk), we will additionally include a random intercept at the infant level to incorporate repeated measurements within the infant.

In case there is no appropriate fit of the infant-level mixed-effects regression model for one of the endpoints, we will replace this analysis for a cluster-level analysis, in which we aggregate outcomes at the cluster level and compare these using an equivalent covariate-adjusted residual estimator to take into account cluster-level and infant-level covariates.[14-16] For the endpoints derived from PPSs we will first consider aggregation at the level of the PPS before further simplifying to cluster-level aggregation. Otherwise, if the model assumptions are not violated, we will perform these cluster-level analyses of primary and secondary outcomes as sensitivity analyses, i.e. to check for robustness of the result of the analysis. We will perform two additional sensitivity analyses: one in which we only include the allocated intervention group as the determinant of interest, and one in which we only include time in months since start of intervention period as the determinant of interest.

For outcomes that are collected at the cluster-aggregated level (surveillance-based neonatal severe infection/sepsis and major non-infection neonatal morbidity), cluster-level analysis is the primary and only approach. As no time resolution within the intervention period is available for these outcomes, only the allocated intervention will be included as determinant of interest.

Any deviations from this approach will be reported as unplanned analyses.

7.2.3 Analysis details for primary and secondary outcomes

Analysis details for all primary and secondary outcomes are listed in X†: data relevant for the composite outcome of major non-infection neonatal morbidity

O: indicates electronic data capture system and forms to be used

Supplement Table 2 and include details on the planned level of analysis, statistical method, outcome measure, determinants of interest, fixed covariates, random effects, measure of association, sensitivity analyses and subgroup analyses. In addition, we will describe here the analysis details for the primary (neonatal severe infection/sepsis), main secondary outcome (resistant bacterial colonisation) and the secondary cluster-aggregated outcomes (surveillance-based neonatal severe infection/sepsis and major non-infection neonatal morbidity). Other secondary endpoints are analysed in similar manners and are therefore not additionally detailed here.

Neonatal severe infection/sepsis

We will compare the cumulative incidence of neonatal severe infection/sepsis in infants in the intervention arm compared to the control arm using a mixed-effects logistic regression model, with random intercept for cluster. The two determinants of interest are allocated intervention group and time in months since end of the wash-in period (being zero for control hospitals). We will include co-variates used for restricted randomisation (cluster-level aggregated data from the baseline period) at the cluster level, to adjust for cluster-level variation. In addition, we will include birth weight, gestational age, and mode of delivery (vaginal birth or caesarean section) at the infant level to adjust for these covariates. The result will be reported as odds ratio with 95% confidence interval. We will perform a subgroup analysis in extremely premature infants (born before 28 weeks of gestational age) and non-extremely premature infants (born at or after 28 weeks of gestational age).

Resistant bacterial colonisation

We will compare the proportion of infants colonised during PPSs in the intervention arm to the control arm using a mixed effects time-series analysis, with random intercept and random time-slope at the cluster level and random intercept at the infant-level. The two determinants of interest are allocated intervention group and time in months since end of the wash-in period (being zero for control hospitals). We will include co-variates used for restricted randomisation, birth weight, gestational age, and mode of delivery (vaginal birth or caesarean section). The result will be reported as odds ratio with 95% confidence interval. We will perform a subgroup analysis in extremely premature infants (born before 28 weeks of gestational age) and non-extremely premature infants (born at or after 28 weeks of gestational age).

Secondary cluster-aggregated outcomes

We will compare the cluster-level cumulative incidence of surveillance-based neonatal severe infection/sepsis and major non-infection neonatal morbidity between the intervention and control arm. As these outcomes are collected at the cluster-aggregated level, these analyses will follow the cluster-level approach using the covariate-adjusted residual estimator as described in section 6.2.2, with the allocated intervention as the determinant of interest. For both outcomes, we will adjust for the baseline cluster-level value of the same outcome. As no individual-level data are available for these analyses, adjustment for infant-level covariates is not possible.

7.2.4 Exploratory outcomes

We will define parameters needed to model acquisition of resistant colonisation in infants in both intervention and control clusters, e.g. colonisation pressure on the unit over time, number of high-risk and non-high-risk infants hospitalized at the unit and duration of hospitalization. We will subsequently develop a mathematical model that best describes acquisition of resistant colonization using these

parameters and compare acquisition of resistant colonisation between the intervention and control arm.

We will explore the effect of the intervention among high-risk infants on cumulative incidences of laboratory confirmed bloodstream infection with a relevant multidrug resistant pathogen, SSIs, including superficial, deep or organ-space SSI, and DAIs. In addition, we will compare days on antibiotic treatment per antibiotic substance groups and the prevalence of breastfeeding and mother's milk intake and days with human milk intake among high-risk infants in both groups.

7.3 MISSING DATA

We intend to collect complete clinical data from all enrolled infants and have a monitoring plan in place to prevent missing data (see Section 6.4). If there are missing data in any of the covariates used in the regression, these will be handled using multiple imputation. Missing data on clinical outcomes (e.g. occurrence of sepsis) are expected to be rare and will not be imputed.

Stool sampling is planned 1- or 4-weekly during cross-sectional point prevalence surveys (PPS) and is dependent on production of stool of infants at the unit. We therefore anticipate missing data for resistant bacterial colonisation. For the analyses on resistant bacterial colonisation, we will use two approaches. The primary approach is to perform only complete case analysis per PPS, i.e. ignoring non-collected or non-analysed samples. We will explore the validity of this approach by using a two-step imputation approach. First, based on last observation carried forward (LOCF), infants with a previous PPS result showing resistant bacterial colonisation prior to the missing PPS will be imputed deterministically to be colonised. This is in line with the assumption that it is unlikely infants lose their resistant bacterial colonisation during the same admission. Next, using multiple imputation by chained equations, we will impute missing data on resistant bacterial colonisation for all other missing PPS.

7.4 SAFETY

For the assessment of safety during the study we refer to the study protocol.

7.5 INTERIM ANALYSES

There are no interim analyses planned.

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9 SUPPLEMENT

9.1 SUPPLEMENT TABLE 1

Overview of data collection approaches for required endpoints

Endpoint	Relevant for which outcome type				Instrument		
	Main study				DHIS2	REDCap	
	1°	2°	Exploratory	Implementation		PPS	Unit-level
Infection outcomes							
Neonatal severe infection/sepsis	X	X			O		
Resistant bacterial colonisation		X				O	
Laboratory-confirmed bloodstream infection		X			O		
Clinical sepsis		X			O		
Pneumonia		X			O		
Necrotising enterocolitis		X			O		
Antibiotic use		X			O	O	
Laboratory-confirmed bloodstream infection with multidrug-resistant pathogen			X		O		
Surgical Site Infection			X		O		
Device-associated infection			X		O		
Other neonatal outcomes							
Neonatal unit mortality		X			O		
Length of stay		X			O		
Medically or surgically treated ROP		X†					O
Grade III or grade IV (high-grade) IVH		X†					O
Cystic PVL							O
BPD of any grade at 36 weeks' post-menstrual age		X†					O
Breastfed/mother's milk intake			X			O	
Human milk intake			X		O		
Implementation outcomes (infant-level)							
Receipt of minimum expected target duration of StSC		X		X		O	
Number of minutes/hours of StSC per 24h		X		X		O	

X†: data relevant for the composite outcome of major non-infection neonatal morbidity

O: indicates electronic data capture system and forms to be used

9.2 SUPPLEMENT TABLE 2

Overview of statistical methods for trial endpoints

Endpoint	Level of analysis	Statistical method	Outcome measure	Determinants of interest	Fixed covariates	Random effects	Measure of association	Sensitivity analysis	Subgroup analyses
Neonatal severe infection/sepsis	Primary analysis: at infant level	Mixed-effect logistic regression	Cumulative incidence	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for control clusters)	Birth weight, gestational age, and mode of delivery (vaginal birth or caesarean section)	Random intercept at cluster level	Odds ratio with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest 3. Only include time in months since start of intervention period as the determinant of interest	Gestational age before 28 weeks versus at or after 28 weeks
Resistant bacterial colonization 1. Overall 2. Extended-spectrum beta-lactamase 3. Carbapenemase 4. Vancomycin resistance in enterococci	Primary analysis: at infant level	Mixed-effect time series	Prevalence	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for control clusters)	Birth weight, gestational age, and mode of delivery (vaginal birth or caesarean section)	1. Random intercept and random time-slope at cluster level 2. Random intercept at the infant-level	Odds ratio with 95% confidence interval	1. Analysis at the PPS level, or alternatively the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest 3. Only include time in months since start of intervention period as the determinant of interest	Gestational age before 28 weeks versus at or after 28 weeks (for overall resistant colonization only)
Clinical sepsis **LC-BSI** **Pneumonia**	Primary analysis: at infant level	Mixed-effect logistic regression	Cumulative incidence	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for	Birth weight, gestational age, and mode of delivery (vaginal birth or caesarean section)	Random intercept at cluster level	Odds ratio with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest	

Endpoint	Level of analysis	Statistical method	Outcome measure	Determinants of interest	Fixed covariates	Random effects	Measure of association	Sensitivity analysis	Subgroup analyses
NEC				control clusters)				3. Only include time in months since start of intervention period as the determinant of interest	
Neonatal severe infection/sepsis **LC-BSI** **Clinical sepsis**	Primary analysis: at infant level	Mixed-effect Poisson regression (or negative binomial) with the log(number of admission days) during the intervention period as an offset	Incidence rate	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for control clusters)	Birth weight, gestational age, and mode of delivery (vaginal birth or caesarean section)	Random intercept at cluster level	Incidence rate ratio with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest 3. Only include time in months since start of intervention period as the determinant of interest	
Surveillance-based neonatal severe infection/sepsis	At the cluster level	Mixed-effects Poisson regression (or negative binomial) with the log(total number of admissions) as the offset	Cumulative incidence	The randomly allocated intervention	Baseline cluster level surveillance-based neonatal severe infection/sepsis (log probability of the endpoint)	N.A.	Incidence rate ratio with 95% confidence interval		

Endpoint	Level of analysis	Statistical method	Outcome measure	Determinants of interest	Fixed covariates	Random effects	Measure of association	Sensitivity analysis	Subgroup analyses
Major non-infection neonatal morbidity	At the cluster level	Mixed-effects Poisson regression (or negative binomial) with the log(total number of admissions) as the offset	Cumulative incidence	The randomly allocated intervention	Baseline cluster level major non-infection neonatal morbidity (log probability of the endpoint)	N.A.	Incidence rate ratio with 95% confidence interval		
Neonatal unit mortality	Primary analysis: at infant level	Mixed-effect logistic regression	Mortality (risk)	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for control clusters)	Birth weight, gestational age, mode of delivery (vaginal birth or caesarean section) and baseline cluster level neonatal unit mortality (log odds of the endpoint)	Random intercept at cluster level	Odds ratio with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest 3. Only include time in months since start of intervention period as the determinant of interest	
Neonatal unit length of stay	Primary analysis: at infant level	Marginal Fine-Gray model with neonatal death as competing event [17]	Time in days until discharged alive	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for	Birth weight, gestational age, mode of delivery (vaginal birth or caesarean section) and baseline cluster level length of stay (log	Random intercept at cluster level	Absolute difference in number of admission days with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Cox proportional hazards regression to estimate the cause-specific hazard ratio instead of sub-	

Endpoint	Level of analysis	Statistical method	Outcome measure	Determinants of interest	Fixed covariates	Random effects	Measure of association	Sensitivity analysis	Subgroup analyses
				control clusters)	probability of the endpoint)			distribution hazard ratio 3. Only include the allocated intervention group as the determinant of interest 4. Only include time in months since start of intervention period as the determinant of interest	
Antibiotic treatment	Primary analysis: at infant level	Mixed-effects Poisson regression (or negative binomial) with the log(total number of calendar days) as the offset	Days on antibiotic treatment	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for control clusters)	Baseline cluster level antibiotic use (proportion of infant days on antibiotic treatment)	Random intercept at cluster level	Incidence rate ratio for number of days on antibiotic treatment with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest 3. Only include time in months since start of intervention period as the determinant of interest	
StSC duration	Primary analysis: at infant-PPS level	Mixed-effects linear regression Covariate-adjusted residuals estimator	Total duration of StSC in minutes during monthly 24-hour periods	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for control clusters)	Birth weight and gestational age	Random intercept at cluster level	Difference in minutes with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest 3. Only include time in months since start of intervention period as	Neonatal unit country

Endpoint	Level of analysis	Statistical method	Outcome measure	Determinants of interest	Fixed covariates	Random effects	Measure of association	Sensitivity analysis	Subgroup analyses
								the determinant of interest	
StSC target attainment	Primary analysis: at infant-PPS level	Mixed-effects logistic regression	Attainment of the site-level target for daily total duration of StSC per infant (binary yes/no)	1. The randomly allocated intervention 2. Time in months since start of the intervention period (being zero for control clusters)	Birth weight and gestational age	Random intercept at cluster level	Odds ratio for target attainment with 95% confidence interval	1. Analysis at the cluster level using covariate-adjusted residuals estimator[1] 2. Only include the allocated intervention group as the determinant of interest 3. Only include time in months since start of intervention period as the determinant of interest	Neonatal unit country

[1.] In case there is no appropriate fit for infant-level analysis, the cluster-level analysis will replace the primary analysis.

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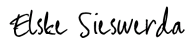
Elske Sieswerda E.Sieswerda@umcutrecht.nl Beveiligingsniveau: E-mailadres, Accountverificatie (verplicht), Ingelogd	 Aanneming van de handtekening Vooraf geselecteerde stijl Handtekening-id: ED1706E6-84E8-4E39-AADC-DC19F33E0F08 IP-adres gebruiken: 143.121.239.227 Met ondertekeningsverificatie via Docusign-wachtwoord Met redenen voor ondertekening (op elk tabblad): Ik heb dit document gecontroleerd	Verzonden: 2-3-2026 08:20:28 Bekeken: 2-3-2026 09:15:21 Ondertekend: 2-3-2026 09:16:22
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