

Study name:

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.

NeoDeco Study

Restricted Randomisation Procedure

Version 2.0 dated 27 Jan 2025

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DOCUMENT HISTORY

VERSION	DATE	SUMMARY OF CHANGES	AUTHOR(S)
Version 1.0	29-Feb-2024	Initial version	Elske Sieswerda (UMCU) C. Henri van Werkhoven (UMCU)
Version 1.1 (draft)	29-Oct-2024	Aggregation methods for variables “Level of StSC” and “Prevalence of resistant bacterial colonization” were aligned with description in “Data collection for Restricted Randomisation procedure within NeoDeco”	C. Henri van Werkhoven (UMCU)
Version 2.0	27 Jan 2025	Colonisation prevalence is changed from co-primary to secondary outcome in line with study protocol.	C. Henri van Werkhoven (UMCU)

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1. Study definitions

Cluster	A cluster is defined as the Neonatal Intensive Care Unit (NICU) or a number of NICUs from one hospital participating in the NeoDECO study.
Restricted randomisation	Restricted randomisation is an adjusted randomization procedure in order to achieve balance between intervention and control arms in a randomized study.

2. Protocol Overview

The NeoDeco study is a pragmatic, multicenter, parallel-group, cluster-randomized, hybrid effectiveness-implementation study that determines the effect of implementation of optimized kangaroo care on neonatal severe infection/sepsis in high-risk infants in the neonatal intensive care unit (NICU). Secondary aims include assessing the effect of optimized kangaroo care on resistant bacterial colonization. High-risk infants born before 32 weeks' gestation and admitted to participating NICUs will be involved in the study, which will take place in 24 NICUs across Europe.

The NICUs will be divided into two staggers. Within each stagger, at least 10 sites will be randomized 1:1 to the intervention or control arm, as described in the following procedure.

Sites in the intervention arm will adopt Skin-to-Skin Contact to optimize KC, as defined in the NeoDeco protocol and the NeoDeco Kangaroo Care procedure manual. Sites in the control arm should follow standard care, including KC and StSC sessions, as per current local practice.

3. Randomisation

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 NICUs will be randomised 1:1 to the intervention or control arm. A subsequent stagger of NICUs will be randomised using the same approach conditional on at least three months of baseline surveillance data collection and 1 month colonization data. The minimum defined number of clusters per stagger is 10.

We will use restricted randomisation to reduce the risk of imbalance between the intervention and control NICUs in baseline characteristics that are associated with the primary outcome (baseline sepsis risk), first secondary outcome (resistant colonisation prevalence) and baseline level of skin-to-skin care (StSC) use at each cluster. 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 NICU and one control NICU.

An independent statistician will randomly select a randomisation sequence from all potential sequences that allow for balance between study arms in these key baseline study characteristics while maintaining sufficient unpredictability and randomness.¹⁻³

4. Covariates included in restricted randomisation procedure

Before NeoDeco starts, we will gather the following baseline cluster-level factor data for the restricted randomization procedure.

- **Neonatal severe infection/sepsis risk.** During the baseline period of 3 months before randomization, we will define the cumulative incidence of neonatal severe infection/sepsis in high-risk infants during their NICU stay. These data will be retrieved from NeolPC surveillance, which runs parallel to NeoDeco in all participating centers.
- **Prevalence of resistant bacterial colonization.** NeoDeco was preceded by a feasibility study (NeolPC colonization assessment phase) to inform the study on the best approach to collect relevant anonymous data and to assess resistant bacterial colonization prevalence. During this 4-week feasibility study, we have defined the prevalence of resistant bacterial colonization based on four point prevalence surveys in high-risk infants in most of the NICUs that will be part of NeoDeco. Resistant colonization prevalence per cluster will be estimated based on the average proportion of admitted high-risk infants with detection of one or more pre-specified bacterial resistance genes in a stool sample during 4 PPS in the study period. Resistant bacterial colonization in high-risk infants is defined as the detection with PCR of one or more pre-specified bacterial resistance genes (based on gene families of CTX-M, SHV, KPC, IMP, NDM, VIM, OXA-48, vanA and vanB) in a faecal sample of a high-risk infant during the feasibility study. A total of 10 study clusters have not participated in the feasibility study. From these clusters, resistant bacterial colonization will be defined based on weekly cross-sectional point-prevalence surveys during the first month of the baseline period.
- **Level of StSC.** We will define average total duration of StSC per day in high-risk infants, based on reported duration of StSC in all point-prevalence surveys obtained during at least the first four weeks of the baseline period.
- **NICU country.**
- **Cluster size.** We will define cluster size as a continuous variable based on most recently available high-risk infant admissions per year per cluster.

5. Restricted randomisation steps

We will take the following steps for the restricted randomization procedure, as described by others.^{2,4,5}

1. We will define all potential random allocations based on unrestricted randomisation and the number of clusters per stagger, using the following formula:

$${}^{2c}C_c = \frac{(2c)!^1}{c! c!}$$

${}^{2c}C_c$ = the number of combinations of 2c clusters allocated to 2 treatment arms each with c clusters where order is not important and repetition is not allowed

c = the number of clusters in each arm

¹ ! represents the factorial function. The factorial of a number is the product of all integers less or equal to that number e.g. 6! = 1 x 2 x 3 x 4 x 5 x 6 = 720

For NeoDeco this would lead to 2.704.156 potential allocation schemes if all clusters would be randomized at once. However, with staggered randomization the number of clusters per stagger is lower. When randomizing 2 staggers of 12 clusters each, there would be a total of **924** potential allocation schemes per stagger. With 10 clusters in one stagger, the number of potential allocation schemes is 252. We have defined 10 clusters per stagger as acceptable minimum.

2. We will score the balance of each possible allocation scheme using a balance metric B . B is the weighted sum of the squared difference in the mean covariate values across both study arms:^{6,7}

$$B = \sum_{c=1}^C \omega_c (\bar{z}_{1c} - \bar{z}_{0c})^2$$

ω_c is the weight for the c^{th} cluster-level covariate (taken to be the inverse variance of the cluster means for the c^{th} covariate); C is the total number of covariates included in the restricted randomization procedure; and \bar{z}_{1c} and \bar{z}_{0c} are the average of the c^{th} cluster-level covariates across intervention and control clusters, respectively.

B will be calculated for the following baseline variables in high-risk infants: neonatal severe infection/sepsis risk, prevalence of resistant bacterial colonization, level of StSC, and cluster size.

3. From all randomization schemes, the smallest set of candidate randomization schemes will be selected, in ascending order of B , such that the following three criteria are met: (1) each pair of clusters has at least 10% chance of being in the same arm and at least 20% chance of not being in the same arm (i.e. sufficiently unpredictable), (2) the size of the set of candidate schemes is at least 80 (i.e. sufficiently random), and (3) each arm includes at least one cluster from each country.
 - If the number of candidate randomization schemes is >40% of the total number of potential random allocations, we will relax these criteria to ensure that the most important factors are well balanced. Relaxation will be done in the following order:
 - o To relax the restriction of a balanced cluster size and recalculate B .
 - o To relax criterion 3 (that each arm includes at least one cluster from each country) for the country or countries with the lowest number of sites per stagger.
4. From this set of candidate randomization schemes, an independent statistician will randomly select one randomisation scheme.

We will repeat the procedure for the second stagger and this randomisation will therefore be independent of randomisation of the first stagger.

6. References

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Final Audit Report

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