NeoCHG

NeoCHG Statistical Analysis Plan

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Revision History

Version	Author	Date	Reason for Revision
Draft 0.1	MC	29/10/2020	First draft – copy of protocol version 1.0
Draft 0.2	MC	03/09/2021	First draft of main SAP
Draft 0.3	MC	27/09/2021	Updated following comments by SW
Draft 0.4	MC	01/10/2021	Updated following initial comments from TMG
Draft 0.5	MC	06/10/2021	Updated following comments by Neal Russell
Draft 0.6	MC	13/10/2021	Updated following comments from DMC, Neal Russell, Mike Sharland, Adrie Bekker and Angela Dramowski
Draft 0.7	MC	19/10/2021	Updated following comments from SW and EG
Draft 0.8	MC	20/10/2021	Updated following MC final review

Contents

1. Trial Design

1.1. Design & outline

NeoCHG is a randomised controlled factorial trial with a 3x2x2+control design enrolling 182 neonates aged 1-6 days old (1-2kg) from two sites in Bangladesh and South Africa. The trial is designed to evaluate the efficacy and safety of different application strategies of antiseptic to reduce bacterial load on the skin of babies.

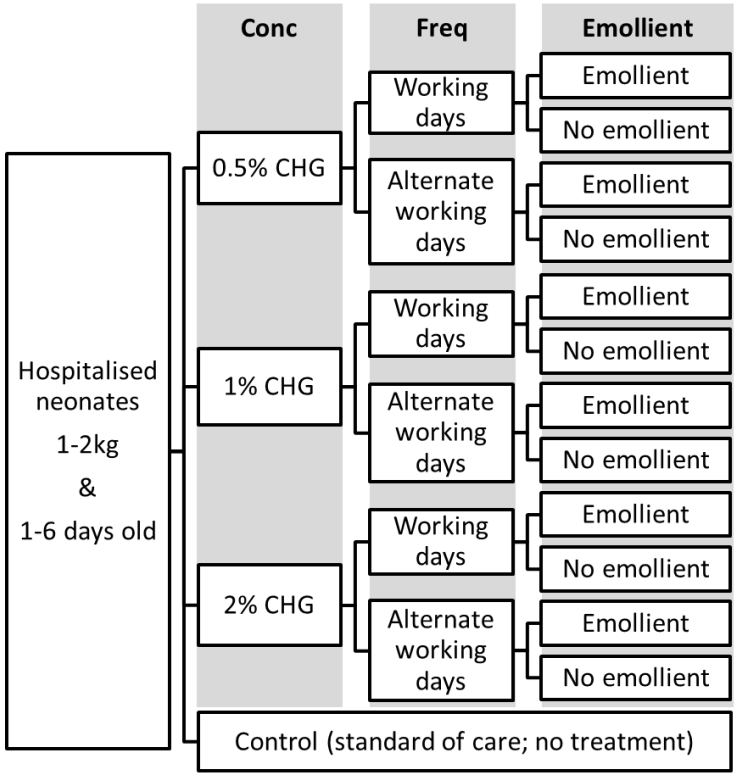
The three factors are:

- Chlorhexidine (CHG) antiseptic concentration: 0.5%, 1% & 2%
- Frequency of application: working days & alternate working days
- Emollient (sunflower oil): emollient applied & no emollient applied

The control group will receive standard of care, although the reference arm will be 0.5% CHG, alternate working days and no emollient as there are more effective replicates of each of the factorial arms and therefore greater power for comparison. 0.5% CHG, alternate working days and no emollient was selected as it would be the most straightforward to implement.

The trial design is summarised in the trial scheme below.

Figure 1: Trial Schema



Note: CHG=chlorhexidine gluconate. Alternate working days are Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday, depending on the standard working pattern in each country.

* Pseudomonas aeruginosa was missing from protocol v1.0. Addition has been clarified to SAHPRA

Follow up to 28 days.
Last application of CHG at day 14 after enrolment or discharge (whichever earlier)

Co-primary outcome(s)

- Change in bacterial load from baseline to final swab (efficacy)
- Adapted Neonatal Skin Condition Score (safety) (absolute score and grade)

Secondary outcomes

- Temperature (change in absolute temperature and grade (hypothermia))
- Acquisition & loss of specific bacterial species
  - Enterobacteriaceae
  - Acinetobacter
  - *Staphylococcus aureus*
  - *Beta haemolytic streptococci (group A and B)*
  - *Enterococcus*
  - *Candida*
  - *Pseudomonas aeruginosa**

1.2. Population

Eligibility to the trial is based on the child meeting all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria

1. Aged 1-6 days (post-natally) at enrolment
2. Gestational age ≥28 weeks at birth
3. Birth weight ≥1000g and <2000g (or current weight if unknown)
4. Parental consent
5. Parent's willingness to avoid routine use of emollients other than those indicated by the randomised allocation

Exclusion criteria

1. Poor skin condition (skin score of 2 or more in any of three domains (see Appendix I in protocol)) at the time of enrolment
2. Known congenital or acquired skin disorder or defect at time of enrolment
3. Anticipated length of hospital stay <7 days
4. Chlorhexidine or emollient application determined inappropriate in the opinion of the enrolling clinician

The primary analysis population is intention-to-treat, including all randomised babies, regardless of treatment received. This corresponds to estimating the impact of the effectiveness of the treatments. However, in secondary analyses we will also use inverse-probability weighting methods to adjust for deviation from randomised strategy if non-compliance rates are >15%, which is a more efficient approach than defining a per-protocol population.

Loss-to-follow up is expected to be low given that expected length of hospital stay under 7 days is an exclusion criteria. Therefore, most babies should have baseline and two subsequent swabs on their allocated regimen. Missing swabs will be monitored and babies without baseline and two post-baseline swabs will be replaced to maintain power. However, all baseline and post-baseline results will be included in analyses.

2. Outcome measures

2.1. Primary outcomes

Co-primary outcome measures

- Skin bacterial load – change in colony forming units (CFUs) in the nose (1 swab), cervical skin folds and umbilicus (1 pooled swab), and peri-rectal area (1 swab) from randomisation (before chlorhexidine application) to D3+/- 1 day and D8 +/- 3 days microbiology data collection (efficacy).
- Modified neonatal skin condition score (see protocol) used before each application of chlorhexidine, or alternate working days in controls (safety). The primary analysis of this

outcome will consider the absolute score. Secondary analysis of this outcome will consider graded toxicity (see protocol)

2.2. Secondary outcomes

Efficacy secondary outcome measures

- Acquisition and loss of specific bacterial species: Enterobacteriaceae, Acinetobacter, Staphylococcus aureus, Beta haemolytic streptococci (group A and B), Enterococcus, Candida, Pseudomonas aeruginosa.

Safety secondary outcome measures

- Temperature after chlorhexidine/emollient: considered both as change from before application to after application (after swabs taken in controls), change from baseline after randomisation, and as graded toxicity
- SAEs

Additional groupings of secondary efficacy outcomes (not in protocol)

- Gram-positive skin bacterial load - change in colony forming units (CFUs) in the nose (1 swab), cervical skin folds and umbilicus (1 pooled swab), and peri-rectal area (1 swab) from randomisation (before chlorhexidine application) to D3+/- 1 day and D8 +/- 3 days microbiology data collection.
- Gram-negative skin bacterial load - change in colony forming units (CFUs) in the nose (1 swab), cervical skin folds and umbilicus (1 pooled swab), and peri-rectal area (1 swab) from randomisation (before chlorhexidine application) to D3+/- 1 day and D8 +/- 3 days microbiology data collection.
- Fungal skin bacterial load - change in colony forming units (CFUs) in the nose (1 swab), cervical skin folds and umbilicus (1 pooled swab), and peri-rectal area (1 swab) from randomisation (before chlorhexidine application) to D3+/- 1 day and D8 +/- 3 days microbiology data collection.
- Acquisition and loss of detectable gram positive pathogens
- Acquisition and loss of detectable gram negative pathogens

Additional groupings of secondary safety outcomes (not in protocol)

- Skin dryness score
- Skin erythema score
- Skin breakdown score

2.3. Sample size calculation

The trial is designed as a permuted block factorial, with one control added per permuted block. 182 neonates in 14 permuted blocks provides 90% power to detect a difference of 0.66 standard deviations (SDs) in log colony counts between concentrations and 0.47 SDs between the different levels of frequency and emollient (two-sided α=0.05) (80% power for 0.58 and 0.41 SDs, respectively). This also provides 90% power to detect a difference of 1.04 SD between each concentration and control, and 0.96 SD between each level of frequency/emollient and control (0.92 and 0.96 SDs at 80% power). Previous studies have found varying effects of chlorhexidine on log

colony counts: a decrease from baseline to 24h of 0.2SD with 1% chlorhexidine in Nepal and 2SDs with 2% chlorhexidine in the USA (1, 2).

2.4. Method of randomisation

Randomisation is stratified by site. This factor has been chosen because of practicality and because it has the potential to modify treatment effects (i.e. lead to interaction) due to variation in clinical management and bacteria profile across sites, meaning forcing balance across the randomised groups is most important for this factor. All other factors should be balanced between groups by the randomisation.

Randomisation lists were prepared by the delegated statistician using blocks of size 13 randomly allocated, stratified by site. Permuted blocks were not chosen as a block size of 26 would contain more than 10% of the anticipated randomisation and would therefore risk greater imbalance in case of any bacterial outbreaks in hospital.

2.5. Estimands

The intervention is the randomised concentrations, frequency of application and presence/absence of emollient.

The patient population is new-born babies, between 1 and 2kg and at least 28 gestational weeks at birth, admitted to hospital and expected to remain in hospital for at least seven days, as defined by the inclusion and exclusion criteria.

The co-primary endpoints are change in skin bacterial colony load and modified neonatal skin score, as defined above. Secondary endpoints are defined above.

The population-level summary which provides a basis for comparison between treatment conditions is the difference in mean colony forming units or skin score adjusted for baseline value.

Anticipated intercurrent events and associated strategy are:

- Loss to follow-up: is expected to be low. Multiple imputation will be used for the primary outcome if rates are above 5%.
- Deviation from randomised strategy: Inverse-probability weighting methods will be used to adjust for deviation from randomised strategy, CHG concentration, emollient and frequency as per protocol if deviation rates are > 15%.

2.6. COVID-19

Eligible patients will be neonates predominantly born within the hospital so risk of COVID-19 will be low. NeoCHG was designed before the COVID-19 pandemic and so there are no explicit statistical mitigation strategies. Rate of positive COVID tests in trial participants and any resulting changes to treatment will be monitored and addressed in the analysis if necessary.

3. Derivation of data to be analysed

3.1. Definition of baseline

Baseline values for all measurements will be those recorded at screening either on the screening and enrolment form, or the day 1 microbiology results from the microbiology log.

3.2. Follow-up timings

Timings of swabs will be:

- Day 3: ± 1 day
- Day 8: ± 3 days

3.3. Loss to follow up

Loss-to-follow up is expected to be low given that expected length of hospital stay under 7 days is an exclusion criteria. Therefore, most babies should have baseline and two subsequent swabs on their allocated regimen. Missing swabs will be monitored and babies without baseline and two post-baseline swabs will be replaced to maintain power. However, all baseline and post-baseline results will be included in analyses.

3.4. Free text

Free text fields in CRFs may be corrected for spelling and further categorised.

4. Statistical Analyses

Information will be presented in tables and may also be presented graphically to aid interpretation.

Recruitment data will be presented as per standard CONSORT diagrams (3). Baseline data tables will be presented overall. Unless stated, post-baseline data tables will be presented aggregated in three ways – by concentration (0.5%, 1%, 2%, control), by frequency (working days, alternate working days), by emollient (with, without). Variables will also be presented by factorial randomisation or arm if there is difference between randomised groups of $p<0.05$, used as a flagging device for imbalance and expected for 1 in 20 characteristics by chance, with p-values from t-tests of differences between means for numeric variables and chi-squared tests or Fisher's exact test if cell values are small for categorical variables.

Statistical tests will use 95% confidence intervals unless otherwise stated. Associated two-sided p-values will be produced but binary conclusions of significant/not significant will not be drawn. As this is a pilot trial and the two co-primary outcomes capture different aspects (efficacy and safety) there will be no adjustment for multiple testing, although interpretation of results will take this into consideration.

All analyses will be included in the interim and final reports unless stated.

4.1. Recruitment & Randomisation

The following metrics will be presented overall:

- Total randomisation, n(% of recruitment per site)
- Randomisation to each CHG concentration: n(%)
- Randomisation to each application frequency: n(%)
- Randomisation to emollient/not: n(%)
- Randomisation to each conc/freq/emollient combination: n(%)
- Eligibility: number and reasons for any children randomised in error and excluded or ineligible children included in the analysis

4.2. Baseline

Neonatal baseline

- Site: n(%) Bangladesh, South Africa
- Sex: n(%) male, female
- Age at randomisation (days): median (IQR)
- Gestational age at birth (weeks): median (IQR)
- Method of determining gestational age: n(%) ultrasound, LMP, other
- Birth weight (g): median (IQR)
- Weight at randomisation (g): median (IQR)
- Total skin score at randomisation: median (IQR)
- Temperature at randomisation (^{o}C): median (IQR)
- Antibiotics since birth at baseline: n(%)
- Any comorbidity: n(%)
    - Prematurity: n(%)

- Hyaline membrane disease/RDS: n(%)
- Sepsis: n(%)
- NEC: n(%)

Maternal baseline

- Received antibiotics during labour y/n/unknown: n(%)
- Mode of delivery: n(%)
- Rupture of membranes before delivery yes – assisted/ yes – spontaneous / no – at C-section/ no – not at C-section: n(%)
- Prolonged rupture of membranes (>18h): n(%)
- Liquor clarity: n(%)
- Treatment for suspected sepsis or chorioamnionitis in mother before delivery: n(%)

4.3. Non-Trial Treatment

- Highest level of ventilation received: n(%) invasive ventilation, non-invasive ventilation (CPAP/BiPAP), High flow nasal cannulae, Nasal cannula oxygen, none
- Umbilical venous catheter at any point: n(%) yes
- Central venous catheter at any point: n(%) yes
- Length of hospital stay to d14: median (IQR)
- Length of hospital stay to d28: median (IQR)

4.4. Trial Treatment

The following metrics will be presented by factor. Note that compliance to CHG dose will not be assessed as patients have individual dose bottles for application.

- Total number of CHG applications: median (IQR)
- Last day of CHG application: median (IQR)
- Number of CHG applications before day 3 swab: median (IQR)
- Number of CHG applications before day 8 swab: median (IQR)
- Emollient applied after CHG application: n(%)
- Temperature taken before CHG application: n(%)
- Skin score assessed before CHG application: n(%)
- Temperature taken after CHG application: n(%)
- Skin score assessed after CHG application: n(%)

4.5. Follow-up

The following metrics will be presented overall:

- Baseline swab: n(%) yes
- Day 3 swab: n(%) yes
- Day 8 swab: n(%) yes
- All three swabs: n(%) yes
- Baseline swab on same day as randomisation: n(%) yes
- Day 3 swab within pre-specified window (± 1 day): n(%) yes
- Day 8 swab within pre-specified window (± 3 days): n(%) yes

- Number of days with skin score assessments: median (IQR)
- Last day of skin score assessment: median (IQR)
- Day 3 skin score assessment within pre-specified window (± 1 day): n(%) yes
- Day 8 skin score assessment within pre-specified window (± 3 days): n(%) yes
- Day 28 follow-up: n(%)
- Length of hospital stay to d14: median (IQR)
- Length of hospital stay to d28: median (IQR)

4.6. Primary outcome analyses

Note that no efficacy outcome data will be presented at the interim analysis. Analyses beyond the focal analysis may not be presented at interim analysis, depending on results from focal analysis.

A summary table will be presented:

- Total log10 CFU at baseline: mean (SD) [N]
- Total log10 CFU at d3: mean (SD) [N]
- Total log10 CFU at d8: mean (SD) [N]
- Change in total log10 CFU from baseline to d3: mean (SD) [N]
- Change in total log10 CFU from baseline to d8: mean (SD) [N]
- Change in total log10 CFU from d3 to d8: mean (SD) [N]
- Skin score at baseline: mean (SD) [N]
- Skin score at d3: mean (SD) [N]
- Skin score at d8: mean (SD) [N]
- Change in skin score from baseline to d3: mean (SD) [N]
- Change in skin score from baseline to d8: mean (SD) [N]
- Change in skin score from d3 to d8: mean (SD) [N]

Focal analysis

- The primary analysis population is intention-to-treat, including all randomised babies, regardless of treatment received
- The outcome variables will be:
    - Efficacy: Change in Total log10 CFU from baseline to swab (d3 or d8)
    - Safety: Change in skin score from baseline to each application
- The efficacy primary analysis will include all randomised babies with baseline and at least one post-baseline measure
- The model will be a mixed effects model
- Fixed effects in the model will be:
    - Concentration (0.5%, 1%, 2%)
    - Frequency of application (week days, alternate week days)
    - Emollient (yes, no)
    - Site (Bangladesh, South Africa)
    - Efficacy outcome only: day of swab (d3, d8)
    - Efficacy outcome only: baseline total CFU (continuous; mfp will be used to assess linearity)
    - Safety outcome only: day of application
    - Safety outcome only: baseline skin score (continuous; mfp will be used to assess linearity)
- Individual will be fitted as a random effect to account for repeated measures within individuals
- Normally distributed errors will be fitted in the first instance. Robust variance estimation will be used
- Comparison of main effects within arms will be assessed using the estimate and 95% confidence interval of the comparison of differences between factors and to control.

- The reference group will be concentration 0.5%, frequency alternate working days and no emollient as this treatment strategy would be the most straightforward to implement. The control will not be used as the reference as the sample size for this arm is lower than for the factorial arms.
- Comparisons between other arms and between arms and the control arm may also be performed. Interpretation will take multiple testing into consideration
- Transformations to the safety endpoint may be performed if there is clear evidence of deviations from normally distributed errors in the safety outcome. If more than 70% of the safety endpoint are in one category, goodness of fit of alternative models (e.g. ordinal) will be considered

Interaction analysis

- Interactions between factorial terms will also be fitted one at a time, in separate models, to assess evidence for the presence of interactions
- Models and reporting of results will be as above

Repeated samples efficacy sensitivity analysis

- Change from baseline to the:
    - first outcome measure after 48h post randomisation
    - final outcome measure

  will also be modelled
- Model and reporting of results will be as the focal analysis except swab will not be fitted as a fixed effect (as there will be one swab only), and individual will not be fitted as a random effect (as there will be no repeated measures among individuals)

Day of sampling efficacy sensitivity analysis

- The focal efficacy analysis described above will be repeated with days since last CHG application fitted as a fixed effect (continuous; mfp will be used to assess linearity)

IV antibiotics efficacy sensitivity analysis

- The initial efficacy analysis described above will be repeated with received IV antibiotics in last 24h/not fitted as a fixed effect (factor)

Inverse weighting

- Inverse-probability weighting methods will be used to adjust for deviation from randomised strategy, CHG application, frequency and emollient application if deviation rates are > 15%. This is a more efficient and less biased approach than defining a per-protocol population (4).

Bayesian analysis

- Primary outcome main analysis will also be conducted in a Bayesian framework.
- Models will be fitted as the initial analyses above
- Sensitivity analysis to prior assumptions will be performed using non-informative, optimistic and sceptical priors (see appendix for details). The analysis will focus on non-informative priors, with informative used as sensitivity analysis, unless there are convergence issues with non-informative priors

- Posterior probability curves will be created for each factor compared to control and between arms within a factor
- The posterior probability of each arm truly being better that the comparator will be calculated for each factor arm compared to control and between arms within a factor

Subgroup analyses

- Subgroup analyses will be:
    - Antibiotic exposure before baseline (postnatal/intrapartum). Binary factor
    - Rupture of membranes. Binary factor
    - Ventilation status at baseline. Binary factor
    - Very Low Birth Weight (<1.5kg). Binary factor
    - Age at recruitment (in days). Fitted as a two groups split at median unless a three group factor (approx. 1/3 of participants in each group) is clearly a better representation of the data
- The main effect will be fitted as above with additional main effect of subgroup. The interaction between subgroup and each factor will also be fitted one at a time, in separate models

4.7. Secondary efficacy outcome analyses

Note that no efficacy outcome data will be presented at the interim analysis.

A summary table will be presented for any focal species, any gram positive pathogens, any gram negative pathogens, and each focal species separately.

- Presence of focal species at baseline: n(%)
- Presence of focal species at d3 swab: n(%)
- Presence of focal species at d8 swab: n(%)
- Presence of focal species at d3 given focal species at baseline: n(%)
- Presence of focal species at d3 given no focal species at baseline: n(%)
- Presence of focal species at d8 given focal species at baseline: n(%)
- Presence of focal species at d8 given no focal species at baseline: n(%)
- Presence of focal species at d8 given focal species at d3: n(%)
- Presence of focal species at d8 given no focal species at d3: n(%)

Presence/absence of focal species analysis

- The analysis will include all randomised babies with baseline and at least one post-baseline swab
- Fixed effects in the model will be:
    - Concentration (0.5%, 1%, 2%)
    - Frequency of application (week days, alternate week days)
    - Emollient (yes, no)
    - Site (Bangladesh, South Africa)
    - Swab (d3, d8)
    - Presence/absence of focal species at baseline

- Individual will be fitted as a random effect to account for repeated measures within individuals
- Binomial generalised linear mixed models will be fitted with logit link
- Margins will be taken for presentation of results
- Comparison of main effects within arms will be assessed using the estimate and 95% confidence interval of the comparison of differences between factors and in comparison, to control.
- If prevalence rates are low, day 3 and day 8 swabs will be modelled separately using exact logistic regression

Additional analyses, as per the primary outcomes, may also be performed.

Secondary bacterial load analyses

Summary tables and focal analyses for gram positive, gram negative bacterial and fungal skin load will be presented as per the primary efficacy focal analysis. Additional analyses, as per the primary outcome, may also be performed.

4.8. Secondary safety outcome analyses

A summary table will be presented for all babies randomised to treatment groups:

- Temperature at baseline: mean (SD) [N]
- Temperature at d3 pre-application: mean (SD) [N]
- Temperature at d3 post-application: mean (SD) [N]
- Temperature at d8 pre-application: mean (SD) [N]
- Temperature at d8 post-application: mean (SD) [N]

Temperature changes from baseline

- The analysis will include all babies randomised to treatment with at least one CHG application. Babies in the control group will be excluded from the analysis.
- Two outcome variables will be assessed in different models:
    - Change in temperature from baseline to post application
    - Change in temperature from pre to post application
- Fixed effects in the model will be:
    - Concentration (0.5%, 1%, 2%)
    - Frequency of application (week days, alternate week days)
    - Emollient (yes, no)
    - Site (Bangladesh, South Africa)
    - Day of trial
    - Temperature at baseline (in baseline change model) /pre application (in pre application model) (continuous; mfp will be used to assess linearity)
- Individual will be fitted as a random effect to account for repeated measures within individuals
- Normally distributed errors will be fitted

- Comparison of main effects within arms will be assessed using the estimate and 95% confidence interval of the comparison of differences between factors and in comparison, to control.
- The reference group will be concentration 0.5%, frequency alternate working days and no emollient as this treatment strategy would be the most straightforward to implement.

Additional analyses, as per the primary outcomes, may also be performed

AEs and SAEs

SAEs and AEs will be presented overall and split by MedDRA System Order Class (SOC) and Preferred Term (PT). AEs and SAEs will be displayed as n(%)M where M is the number of events experienced for all children experiencing at least one event (M>n).

- SAEs: n(%)M
- CHG related SAEs: n(%)M
- Emollient related SAEs: n(%)M
- Grade 3 or 4 AEs: n(%)M
- Grade 3 or 4 skins scores (appendix I of protocol) : n(%)M
- Grade 3 or 4 hypothermia (section 6.3 of protocol) : n(%)M

AE and SAE analysis

- Frequency of SAEs will be compared using exact logistic models
- Time-to-event models will be used if AEs occur in >10% of the trial population overall

Secondary components of skin score analysis

Summary tables and focal analyses for individual components of skin score will be presented as per the primary efficacy focal analysis. Additional analyses, as per the primary outcome, may also be performed.

5. References

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2. Sankar M, Paul V, Kapil A, Kalaivani M, Agarwal R, Darmstadt G, et al. Does skin cleansing with chlorhexidine affect skin condition, temperature and colonization in hospitalized preterm low birth weight infants?: a randomized clinical trial. Journal of Perinatology. 2009;29(12):795-801.
3. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Trials. 2010;11(1):1-8.
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5. Dramowski A, Pillay S, Bekker A, Abrahams I, Cotton MF, Coffin SE, et al. Impact of 1% chlorhexidine gluconate bathing and emollient application on bacterial pathogen colonization dynamics in hospitalized preterm neonates–A pilot clinical trial. EClinicalMedicine. 2021;37:100946.

6. Appendix: Bayesian priors

6.1. Non-informative priors

Non informative priors were selected to capture a wide range of possible values.

- Intercept mean =4, sd = 50
- Difference mean =0, sd = 20

6.2. Informative priors (optimistic and sceptical)

Informative priors were determined based on Dramowski et al NeoCOLONIZE (5) data and expert clinician opinion (Adrie Bekker, Angela Dramwoski and Neal Russell) during an online meeting on 12/10/2021. There is a lack of robust data to support the use of strong priors, especially with inclusion from data from a different setting in Bangladesh. Johnson et al (1, 2) was not thought to be suitable as gram negative bacteria was not detected, which NeoCHG is expecting to detect.

Intercept specification

The intercept (1% CHG applied on weekdays with no emollient) was selected as prior data from NeoCOLONIZE could be used. Using mean values from the study and approximations of sd with a multiplier on the sd to capture extra uncertainty, the intercepts will be specified as following a normal distribution with parameters:

- Log CFU: mean 3.5; standard deviation 1; multiplier 3
- Skin score: mean 4.6; standard deviation 0.8; multiplier 2

A higher multiplier was chosen for log CFU as it expected to be more variable over time and sites than skin score. Priors may be reformulated to a reference of 0.5%CHG/alternate weekday/no emollient before analysis to match reference specification in focal analysis.

Difference specification

Clinicians specified the mean difference that optimistic and sceptical persons knowledgeable on the topic might assume, using a reference of 1% CHG applied on weekdays with no emollient. The approach taken was that both optimistic and sceptical persons were assumed to have some belief that the opposing view could be correct, given the assumption of equipoise for the trial to be able to go ahead. The mean values selected were:

Log CFU colony count

Parameter	Optimistic mean	Sceptical mean
0.5% CHG	Higher by 0.5	No effect
2% CHG	Lower by 0.5	No effect
Emollient	0	Higher by 0.5
Alternate day application	Higher by 0.5	No effect

Control	Higher by 1	No effect

Skin score

Parameter	**Optimistic mean**	**Sceptical mean**
0.5% CHG	No change	Improves by 0.5 (-0.5)
2% CHG	No change	Worsens by 1 (+1)
Emollient	Improvement of 1.5 (-1.5)	No change
Alternate day application	No change	Improves by 0.5 (-0.5)
Control	No change	Improvement by 1 (-1)

Differences were specified to follow a Normal distribution with mean as above and 2.5% of the distribution more extreme than the opposing value (sceptical for optimistic priors and optimistic for sceptical priors). This equates to a Normal distribution with:

- Mean = optimistic or sceptical mean
- sd = abs(sceptical mean – optimistic mean)/1.96

Where 1.96 is the critical value from the t-distribution with infinite degrees of freedom.