FULL/LONG TITLE OF THE STUDY	**Neonatal Antimicrobial Resistance and Outcome (neoAMRO)**
SHORT STUDY TITLE / ACRONYM	**Neonatal Antimicrobial Resistance and Outcome (neoAMRO)**
PROTOCOL VERSION NUMBER AND DATE	**V5** **18.10.2022**
IRAS Number:	**268175**
JRES Reference Number	**2019.0048**
Funder Reference Number:	**ANTSRG 04/2018**
This protocol has regard for the HRA guidance and order of content	

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

Date:
18/10/2022

Name (please print):

Sam Hollingworth

Position: Research Governance and Facilitation Officer

Chief Investigator:

Date:
18/10/2022

Signature:
.....

Name: (please print):

...Paul Heath.....

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KEY STUDY CONTACTS	
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Funder(s)	Antibiotic Research UK Genesis 5, York Science Park Church Lane Heslington York YO10 5DQ

STUDY SUMMARY	
Study Title	Neonatal Antimicrobial Resistance and Outcome (neoAMRO)
Internal ref. no. (or short title)	neoAMRO
Study Design	The neonIN surveillance network captures data on episodes of invasive neonatal infection on a web-based database (www.neonin.org.uk). Over 30 UK neonatal units currently contribute to this database in real-time. An episode of neonatal infection is defined as a positive culture collected from a normally sterile site such as the blood, cerebrospinal fluid (CSF) or urine (via catheter or suprapubic aspirate) for which clinicians prescribed at least five days of appropriate antibiotics. Clinical, demographic and microbiological data (including antimicrobial susceptibilities) are collected using a standardised online questionnaire, and denominator data regarding the total number of live-births and neonatal-admissions are collected for each neonatal unit. For the purpose of this study, we will request information on the baby's status (alive/died/not known) at 28 days after the positive culture was obtained. If the baby is alive, then this baby becomes eligible as a control. If the baby has died, then further details will be sought including the date of death and whether death was attributed to the infection. Babies with positive cultures, who have died before receiving 5 days of appropriate antimicrobial therapy (currently a component of the surveillance case definition), will also be captured prospectively.
Study Participants	Infants on participating NNUs who have an episode of infection with a positive culture
Planned Size of Sample (if applicable)	Up to 800
Planned Study Period	Recruitment Period: June 2019 – 30th September 2023 End of Study: 29th February 2024
Research Question/Aim(s)	**Primary aims** • To identify the infections leading to death in babies on UK neonatal units. • To define the clinical characteristics of babies dying from infections. • To describe the management of babies dying from infections with a specific focus on their antimicrobial treatment and the antimicrobial resistance profiles of the causative organisms.
	Secondary aims In a case-control study to assess the hypothesis that babies who die from bacterial infections on neonatal units do so because they receive inappropriate antibiotic management. To do this, babies who die from confirmed bacterial infections will be compared with babies who survive bacterial infections on a range of factors including appropriateness, dose and timeliness of antibiotic use.

FUNDING AND SUPPORT	
FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Antibiotic Research UK (ANTRUK)	**£4,000 over 36 months**

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

PROTOCOL CONTRIBUTORS

Prof Paul Heath and Dr Christina Kortsalioudaki (St. George's University of London) conceived the study; Dr Christina Kortsalioudaki and Dr Eva Galiza initiated the study design and helped with implementation and will conduct primary statistical analysis. St. George's, University of London is the grant holder. All authors contributed to refinement of the study protocol and will approve the final manuscript.

STUDY TIMELINE

Key Objective	Measure of objective	Objective end point date
Application for modification of ethics permission for neonIN database	ethics approval	June 2018
Adaptation of on-line neonIN database	neonIN database adapted for new data	June 2018
Meeting of neonIN teams	meeting	July 2019
Set up of neoAMRO sites	preparation to start data collection	August 2019
On-line data collection commences	data entries	August 2019
Formal review of neonIN/neoAMRO data collection progress at 30 months	completeness of data, number of deaths recorded (>10)	February 2022
Formal review of neonIN/neoAMRO data collection at 36 months	completeness of data, number of deaths recorded (>40)	August 2022
neonIN /neoAMRO data collection completed at 49 months	completion of data entry	September 2023
analysis of all data and study report	study report completion	February 2024

ABBREVIATIONS	
AE	Adverse Event
AR	Adverse Reaction
BSI	Blood Stream Infection
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
GNB	Gram-Negative Bacteria
HCAI	Healthcare Associated Infection
HRA	Health Research Authority
ICF	Informed Consent Form
ICU	Intensive Care Unit
ISF	Investigator Site File
JRES	Joint Research and Enterprise Services
LOS	Late-Onset Sepsis
MRGNB	Multi-Resistant Gram-Negative Bacteria
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health Research
NNU	Neonatal Unit
PI	Principal Investigator
PIDRG	Paediatric Infectious Diseases Research Group
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCU	Special Care Unit
SGUL	St Georges, University of London
SGHFT	St Georges, University Hospitals NHS Foundation Trust
SOP	Standard Operating Procedure
TMF	Trial Master File

STUDY PROTOCOL

Neonatal Antimicrobial Resistance and Outcome (neoAMRO)

1 BACKGROUND

In 2011 we undertook a detailed analysis of death certificates over a 3 year period (England and Wales) and identified infection as the cause of 11% of neonatal deaths [1]. Where a pathogen was identified, 81% were bacterial, 11% were fungal and 9% were viral. The presentation of neonatal infection is non-specific therefore antimicrobial treatment is commenced before a causative organism is identified (called empiric therapy). The antimicrobial resistance patterns of the bacteria causing infections in our neonatal infection surveillance network (neonIN) show that there is a mismatch between recommended empiric antibiotics and the susceptibilities of relevant pathogens in a significant proportion (5-16%) [2,3]. The implication of these findings is that when the "wrong" empiric antibiotic combination is used to treat an infection the infant will be untreated until this is recognised and this may lead to a poor outcome, including death. For example, in a recent neonIN analysis of 118 episodes of Gram-negative neonatal infection, the 10 day attributable mortality was 18%, but this increased to 100% in those with strains resistant to gentamicin (a commonly used antibiotics in empiric regimens) (3/3) [4].

2 RATIONALE

Infections are an important cause of deaths in babies during their first weeks of life. Infection is typically non-specific in presentation. This means clinicians must start antibiotics early and "guess" which antibiotics to use. We know from our surveillance network that in 10-20% of cases the antibiotics chosen will not be the correct ones. A small study showed that when this mismatch occurred the babies had a high mortality. We wish to collect information on neonatal infections, identify the pathogens associated with deaths and determine if gaps in optimal antibiotic treatment are related or lead to poor outcomes.

3 THEORETICAL FRAMEWORK

Through our study we aim to understand and describe better those infections and risk factors that lead to death. The case-control study will enable us to determine if gaps in optimal management, such as the wrong antibiotic or the wrong dose, are associated with poor outcomes. We can then translate such information into practice and develop / improve clinical guidance in order to improve outcomes.

4 RESEARCH QUESTION/AIM(S)

4.1 Primary aims

- To identify the infections leading to death in babies on UK neonatal units.
- To define the clinical characteristics of babies dying from infections.
- To describe the management of babies dying from infections with a specific focus in their antimicrobial treatment and the antimicrobial resistance profiles of the relevant organisms.

4.2 Secondary aim

- In a case-control study we will assess the hypothesis that babies who die from bacterial infections on neonatal units do so because they receive inappropriate antibiotic management. To do this we will compare babies who die from bacterial infections with babies who survive bacterial infections on a range of factors including appropriateness, dose and timeliness of antibiotic use.

5 STUDY DESIGN and METHODS of DATA COLLECTION and DATA MANAGEMENT

5.1 Study Design

This an observational study and no additional interventions will be performed

5.2 Methods

The neonIN surveillance network captures data on episodes of invasive neonatal infection on a web-based database (www.neonin.org.uk). Over 30 UK neonatal units currently contribute to this database in real-time. An episode of neonatal infection is defined as a positive culture collected from a normally sterile site such as the blood, cerebrospinal fluid (CSF) or urine (via catheter or suprapubic aspirate) for which clinicians prescribed at least five days of appropriate antibiotics. Clinical, demographic and microbiological data (including antimicrobial susceptibilities) are collected using a standardised online questionnaire. Denominator data regarding the total number of live-births and neonatal-admissions are collected for each neonatal unit.

For the purpose of this study data will be entered ontoan electronic data collection tool or web based database related to information on the baby's status at 28 days after the positive culture was obtained.

If the baby is alive, then this baby becomes eligible as a control. If the baby has died, then further details will be sought including the date of death and whether the infection was associated with the baby's death. Babies with positive cultures, but who have died before receiving 5 days of appropriate antimicrobial therapy (currently a component of the surveillance case definition), will also be captured prospectively.

5.3 **Data collection**

Invasive infection episodes will be captured prospectively on a web-based infection surveillance database called neonIN (www.neonin.org.uk) which is coordinated by Professor Paul Heath at St George's University of London. The neonIN network currently includes 30 NNUs. For the purposes of this project all centres that wish to participate in neoAMRO will have access to the electronic data collection tool or web based database and will capture anonymised data regarding invasive episodes of infection.

For the purposes of the neoAMRO study, information on the baby's status at 28 days after the positive culture will be collected (alive / died / not known). If the baby is alive, then this baby becomes eligible as a control. However, if the baby has died, then further details will be sought including the date of death and whether the infection was believed to be associated with the baby's death. Babies with positive cultures but who have died before receiving 5 days of appropriate antimicrobial therapy (currently a component of the surveillance case definition), will also be captured prospectively.

Thus, the following data will be collected as part of the neoAMRO study:

- outcome at 28 days (alive / died / not known)
- date of death
- cause of death (if association with infection)
- antibiotics: name / start date / dose / frequency / stop date
- whether antibiotic regime was changed during therapy
- reason for change in antibiotic regime
- new antibiotics: name / start date / dose / frequency / stop date

5.4 **Data Handling**

All data should be handled in accordance with the Data Protection Act 2018 (UK implementation of the EU General Data Protection Regulation (GDPR)).

Dr Adam Witney will be the responsible individual within St George's University of London. The study database will be stored on the server of St George's, University of London with the following technical specifications:

Security:

External website access is governed by a L7 application firewall, with additional host based firewall security. Administrative access to the server is via PKI (Public Key Infrastructure), not username and password, and is for nominated individuals only, authorised by the data holder. Access to the website is via a 256bit SSL certificate backed by a 4092bit server key.

Backup and DR:

System backup is performed by both a grandfather-father-son scheme and a host based FIFO imaging rotation. DR facilities at SGUL includes offsite replication and restoration of services at a secondary data centre. Users will have password controlled access to their own institution data, managed by a small number of administrator users located at SGUL. Regular full database dumps will be performed daily and encrypted on disk using a 4096bit key.

The electronic data collection tool will be password protected and stored securely on servers at St George's University of London and at participating sites. The study ID log which will link patient details to the study will be held only at the participating site.

6 STUDY SETTING

This is a multicentre observational study involving NNUs across the UK. Study personnel (Neonatologists and research Nurses) from these NNUs will identify eligible babies in whom a positive culture has been obtained. The local study teams will then enter the relevant details will be entered onto an electronic data collection tool or web based database, as part of their routine clinical duties. Data will be entered retrospectively on a regular basis either (weekly/monthly) depending on the unit activity and in compliance with the duties of the local team.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

There will be no exceptions (waivers) to eligibility criteria for data inclusion into the study.

The criteria have been carefully considered and are standards used to ensure the data can be appropriately selected, collected and appropriately analysed. It is therefore vital exceptions are not made to the following detailed selection criteria.

- Infants on participating NNUs who have an episode of infection with a positive culture.

7.2 Sampling

7.2.1 Size of sample

Based on our previous data collection (see ref. 2), at the end of the enhanced study period we would expect to have data on up to 800 babies with invasive neonatal infections, approximately 50% will be due to coagulase negative staphylococci (CoNS), approximately 25% will be early onset sepsis and approximately 200 will be Gram-negative sepsis. Based on our recent data for case fatality rates (18% for Gram-negative bacteraemia, 8% for Group B streptococcus, 5% for staphylococcal aureus), we would expect around 50 deaths in this cohort.

All babies who have died within 28 days of a positive culture will then be compared with babies who have survived at 28 days across a range of relevant clinical and demographic factors. For all cases and for two controls per case (selected centrally, based on birth in same birthweight category and in same hospital), this will be performed through collection of anonymised data including birth gestation, birth weight and age at infection, antimicrobials administered for that infection episode (and if changed), relapses, length of stay and attributable mortality at 10 days using a standardised case report form. With approximately 50 cases of death and 100 controls, we anticipate that we will be able to explore the relationship between initial antimicrobial therapy and isolate susceptibility, with outcome, with great certainty. For example, with this sample size we can demonstrate a difference between susceptibility to empiric antibiotics of 80% among cases (or less) to 95% among controls, with 95% significance and 80% power; a difference that is clinically meaningful. A 10-day cut-off for attributable mortality will be used as early mortality is assumed to be more likely a direct consequence of infection than late mortality. Other risk factors for death will be assessed in univariate and multivariable logistic regression analyses.

7.3 Recruitment

7.3.1 Participant identification

Eligible babies are those in whom a positive culture has been obtained. Records will be identified by the local clinical team at each participating unit. The local team consisting of Neonatologists and research Nurses will then enter the relevant details onto an electronic data collection tool or web-based database, as part of their routine clinical duties. Data will be entered retrospectively on a regular basis either (weekly/monthly) depending on the unit activity and in compliance with the duties of the local team.

7.3.2 **Consent**

Informed consent will not be obtained in this study. There will be no change in the routine clinical care of any of the participants and as with the approved neonIN study no written consent will be sought from the individual participants.

7.3.3 **Data collection tool**

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the study database. The Staff Delegation of Responsibilities Log should identify all trial personnel responsible for data collection, entry, handling and managing the database.

7.3.4 **Withdrawal**

In the event where a subject's parents/carer refuse to be included in the study the local team should provide the subject study specific number (as recorded in their local records) to the study team at St George's University of London. The data controller will give the subject number to the data management team at St. George's University of London and request the subject to be removed from the database. Once this action is complete the data controller will inform the local team with a formal letter/email. The local team may communicate this action to the subject's parents/carer.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 **Assessment and management of risk**

This study is an observational study with no change to the clinical care of the study participants. There is therefore no risk to the care of the participant in this study.

Data collection forms in the study database will not bear the participant's name or other directly identifiable data. Only the local clinicians will have access to identifiable data for their patients. The risks associated with a breach of confidentiality are therefore extremely low.

COVID-19 Risk Assessment and Management Strategy

This section applies to all research and should not be amended.

All staff employed by SGUL and/or SGH NHS Foundation Trust are required to complete an ongoing COVID-19 risk assessment prior to undertaking any work on site, which includes research activity. This process is continuously monitored by the responsible line manager.

Participants (unaffected or affected) will not be recruited if they are deemed high risk or are in close contact with someone at risk. The Research Team will contact research participants ahead of scheduled study visits on-site to check for COVID-19 symptoms and the symptom check will be repeated when patients attend the hospital site for the study visit.

Participants will receive information regarding the extra precautions that will be taken in light of the COVID-19 pandemic in the Patient Information Sheet. This will detail steps that patients should take if they have concerns about exposure to COVID-19 through participating in the research, or believe that they are symptomatic or have been in close contact with another person believed to be symptomatic. The Patient Information Sheet will also have contact details for the Research Team for patients to get in touch if they have any concerns or queries about this.

All research personnel are expected to comply with the NHS Trust and University policies on COVID-19.

All patients attending the hospital site for research visits and/or routine clinical follow-up will be expected to abide by the NHS Trust and University policies on COVID-19 which include wearing suitable PPE (provided by the NHS Trust on arrival), adhering to the visitor policy on social distancing and following the one-way routing systems whilst on site.

The schedule of study assessments has been designed so that they align with the current routine clinical pathway for this patient population.

Therefore, research participants and site staff are not perceived to be at any additional risk of exposure to COVID-19 through participation in this research study.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from an appropriate REC for the study protocol and other relevant documents.

For HRA- NHS REC reviewed research

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- It is the Chief Investigator's responsibility to produce the annual reports and submit the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- The Chief Investigator will notify the REC of the end of the study within one year after the end of the study.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Regulatory Review & Compliance

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

Amendments

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

8.4 Patient & Public Involvement

The Patient Information Advisory Group was approached during the design of the neonIN database and their recommendations were considered.

The results will be published and disseminated at conferences, peer reviewed scientific journals and internal reports. Parents of infants can request to receive copies of any publications arising from the database.

8.5 Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

All protocol deviations must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

All data should be handled in accordance with the Data Protection Act 2018 (UK implementation of the EU General Data Protection Regulation (GDPR)).

The participant's trial Identification Number (ID) only, will be used for identification. The Subject ID log can be used to cross reference participant's identifiable information and will be stored securely at participating sites.

1. **Describe the nature of the processing:**

A member of the neonatal team at each centre will be responsible for data collection and data input. As infection cases arise, they will be entered onto an electronic data collection tool or web based database. The central database will be anonymised with subjects identified only by neonIN study number, SEND/BADGER number and date of birth. Once age at infection has been calculated the DOB will be removed from the database. Each participating unit will hold its own secure database in order to link the infants' identifying data with study numbers. All data will be stored in compliance with the Data Protection Act.

2. **Describe the scope of the processing:**

Routine data collected: contributing hospital, DOB (for calculation of age at infection), gender, birth weight, gestation, ward type, date blood culture taken, pathogens isolates, whether the baby received

antibiotics 48 hrs before the culture was taken, whether the mother received antibiotics in the week before delivery, presence of intravenous or arterial lines catheters at time the culture sample was taken, clinical conditions associated with the infection, results of positive cultures including antibiogram, country of the participating unit, date of admission to the neonatal unit, number allocated to the baby on the SEND/Badger database, denominator data from each participating unit to demonstrate the unit activity (number of live births, number of admissions, patient days in NNU, central line days).

The following data to be collected in addition to the neonIN data, as part of the neoAMRO study : outcome at 28 days (alive / died / not known), date of death, cause of death (if association with infection), antibiotics: name / start date / dose / frequency / stop date, whether antibiotic regime was changed during therapy, reason for change in antibiotic regime, new antibiotics: name / start date / dose / frequency / stop date.

The data will be kept for 5 years post study termination/end.

8.7 **Indemnity**

St George's University of London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that St George's has been negligent. This includes negligence in the writing of the protocol, or selection of trial resources.

Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. St George's University of London will not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees.

If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of St George's University of London immediately.

Failure to alert St George's University of London without delay and to comply with requests for information by the sponsor or any designated Agents may lead to a lack of insurance cover for the incident.

8.8 **Access to the final study dataset**

Access to the database is available to all registered neonIN users. neonIN users are not able to identify individual babies or to identify the individual units from which those babies come. Any formal analysis or publication based on the data must first be discussed and approved by the neonIN steering group.

The main analyses (for presentations and publications) will be undertaken by the data controller and the study team at St. George's University of London, on behalf of all the neonIN users.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

Publication: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

Before the official completion of the Trial,

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the **Steering Committee/the Funder** shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.

- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

9.2 Archiving Arrangements

Each site will be responsible for their onsite level study archiving. The trial essential Trial Master File along with any central trial database will be archived at the end of the study in accordance with the sponsor SOP. The agreed archiving period for this trial will be 10 years.

10 REFERENCES

1. Depani SJ, Ladhani S, Heath PT, Lamagni TL, Johnson AP, Pebody RG, et al. The contribution of infections to neonatal deaths in England and Wales. Pediatr Infect Dis J. 2011 Apr;30(4):345-7.

2. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Cailes B, Kortsalioudaki C, Buttery J, Pattnayak S, Greenough A, Matthes J, Bedford Russell A, Kennea N, Heath PT; neonIN network. Arch Dis Child Fetal Neonatal Ed. 2017 Dec 5.

3. Antimicrobial resistance in UK neonatal units: neonIN infection surveillance network. Cailes B, Kortsalioudaki C, Buttery J, Pattnayak S, Greenough A, Matthes J, Bedford Russell A, Kennea N, Heath PT; neonIN network. Arch Dis Child Fetal Neonatal Ed. 2017 Oct 26.

4. Kent A, Kortsalioudaki C, Monahan IM, Bielicki J, Planche TD, Heath PT, Sharland M, Neonatal Gram-Negative MIC group. Neonatal gram-negative infections, antibiotic susceptibility and clinical outcome: an observational study. Arch Dis Child Fetal Neonatal Ed. 2016 Mar 7.

13.3 Appendix 1

Amendment Log				
Amendment No.	**Protocol version no.**	**Date issued**	**Author(s) of changes**	**Details of changes made**
1	2	30/09/2019	St. George's, University of London	1. Addition of participating sites 2. Use of study logo 3. Correction of Sponsor name and address in protocol
2	3.0	05/01/2022	St. George's, University of London	1. Removal of appendix 1 which lists the participating sites 2. Update of study timelines
3	4.0	05/08/2022	St. George's, University of London	1. Update of study timelines 2. Addition of new participating sites 3. Change of PIs at 3 participating sites
4	5.0	18/10/2022	St. George's, University of London	1. Updated wording of protocol to clarify neoAMRO data collection 2. Change of PI at 2 participating sites 3. Addition of new participating site