LONG TITLE OF THE STUDY:

TOPICAL ANALGESIA BEFORE INHALATIONAL ANAESTHESIA: A RETROSPECTIVE OBSERVATIONAL STUDY

SHORT STUDY TITLE / ACRONYM:

TOPICAL ANALGESIA BEFORE INHALATIONAL ANAESTHESIA?

RESEARCH REFERENCE NUMBERS

IRAS Number:	281394
SPONSORS Number:	20AN008
FUNDERS Number:	Not applicable
SPONSOR	Nottingham University Hospitals NHS Trust

PROTOCOL VERSION NUMBER AND DATE:

1.0

07-APR-2020

This protocol has been designed to ensure regard for the HRA guidance

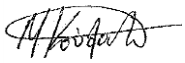
SIGNATURE PAGE

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 publically 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: 03/06/2021

Name (please print): Maria Koufali

Position: Managing Director

Chief Investigator:

Signature:

Date: 07/04/2021

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MATTHEW JAMES BILLINGHAM

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STUDY SUMMARY

Study Title	Topical Analgesia before Inhalational Anaesthesia: A Retrospective Observational Study
Internal ref. no. (or short title)	Topical Analgesia before Inhalational Anaesthesia?
Study Design	Retrospective Observational Study (Cohort design)
Study Participants	Children from 1 month to 18 years of age undergoing elective or urgent inhalational induction of anaesthesia at Nottingham University Hospitals NHS Trust over a six month study period (August 2020 to January 2021)
Planned Size of Sample (if applicable)	1,323
Follow up duration (if applicable)	Not applicable
Planned Study Period	August 2020 to January 2021
Research Question/Aim(s)	To determine whether topical analgesia application prior to receiving inhalational induction of anaesthesia has any beneficial effects for paediatric patients

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**DETAILS OF FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
KATE FROST Head of Patient and Public Involvement and Engagement Nottingham University Hospitals NHS Trust Nottingham Biomedical Research Centre C Floor South Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH 07812 268 438 kate.frost@nuh.nhs.uk	Non-financial support Patient and Public Involvement strategic support Liaison for Nottingham University Hospital Young Person Advisory Group (YPAG)
DOYO ENKI Senior Medical Statistician RDS East Midlands Faculty of Medicine University of Nottingham Nottingham, NG7 2UH 0115 924 9924 (ext 80717) doyo.enki@nottingham.ac.uk	Non-financial support NIHR (National Institute for Health Research) RDS (Research Design Service) East Midlands support advisor

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor will monitor the study conduct against applicable regulatory standards. The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results. The sponsor and funders will be consulted for the final decision/s regarding any aspects of this study.

KEY PHRASES: Topical analgesia

Inhalational anaesthesia

Retrospective observational study

Protocol contributors

CONTRIBUTOR(S) (Names and contact details of ALL individuals providing contribution to the protocol)	DETAILS OF CONTRIBUTION GIVEN
MATTHEW BILLINGHAM Department of Paediatric Anaesthesia Nottingham University Hospitals NHS Trust Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH 07856 246425 mbillingham@doctors.org.uk matthew.billingham@nuh.nhs.uk	Study conceptualisation, design and construction of original protocol Protocol amendments Application for protocol support from Nottingham University Hospitals NHS Trust Patient and Public Involvement and Engagement Team Application for protocol support from Nottingham University Hospitals NHS Trust Research and Innovation department Final protocol completion and authorisation
PAULINE HYMAN-TAYLOR Senior Research Governance Facilitator Nottingham University Hospitals NHS Trust Nottingham Health Science Partners C Floor South Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH 0115 970 9049 pauline.hyman-taylor@nuh.nhs.uk	Protocol reviews, suggestions and amendments
KATE FROST Head of Patient and Public Involvement and	Protocol review, suggestions and amendments (section 8.4 (Patient & Public Involvement))

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DOYO ENKI Senior Medical Statistician RDS East Midlands Faculty of Medicine University of Nottingham Nottingham, NG7 2UH 0115 924 9924 (ext 80717) doyo.enki@nottingham.ac.uk	NIHR (National Institute for Health Research) RDS (Research Design Service) East Midlands support advisor Protocol review and suggestions
CHRISTOPHER TENCH Senior Medical Statistician Faculty of Medicine and Health Sciences Room S/C2711 Medical School University of Nottingham Nottingham, NG7 2UH 0115 823 1419 christopher.tench@nottingham.ac.uk	Protocol reviews, suggestions and amendments (sections 5 and 7 (Study Design and Methods of Data Collection and Data Analysis, Sample and Recruitment)) Peer review (external)
TIM CARD	

Associate Clinical Professor Nottingham Digestive Diseases Centre National Institute for Health Research (NIHR) Biomedical Research Unit Nottingham University Hospitals NHS Trust Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH and Division of Epidemiology and Public Health Faculty of Medicine & Health Sciences University of Nottingham Room B114 Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB 0115 823 1346 tim.card@nottingham.ac.uk	Protocol review and suggestions Review (internal)
JOYCE YEUNG Associate Clinical Professor in Anaesthesia and Critical Care Warwick Clinical Trials Unit Warwick Medical School University of Warwick Gibbet Hill Campus, Coventry, CV4 7AL 02476 573357 j.yeung.4@warwick.ac.uk	Peer review (external)

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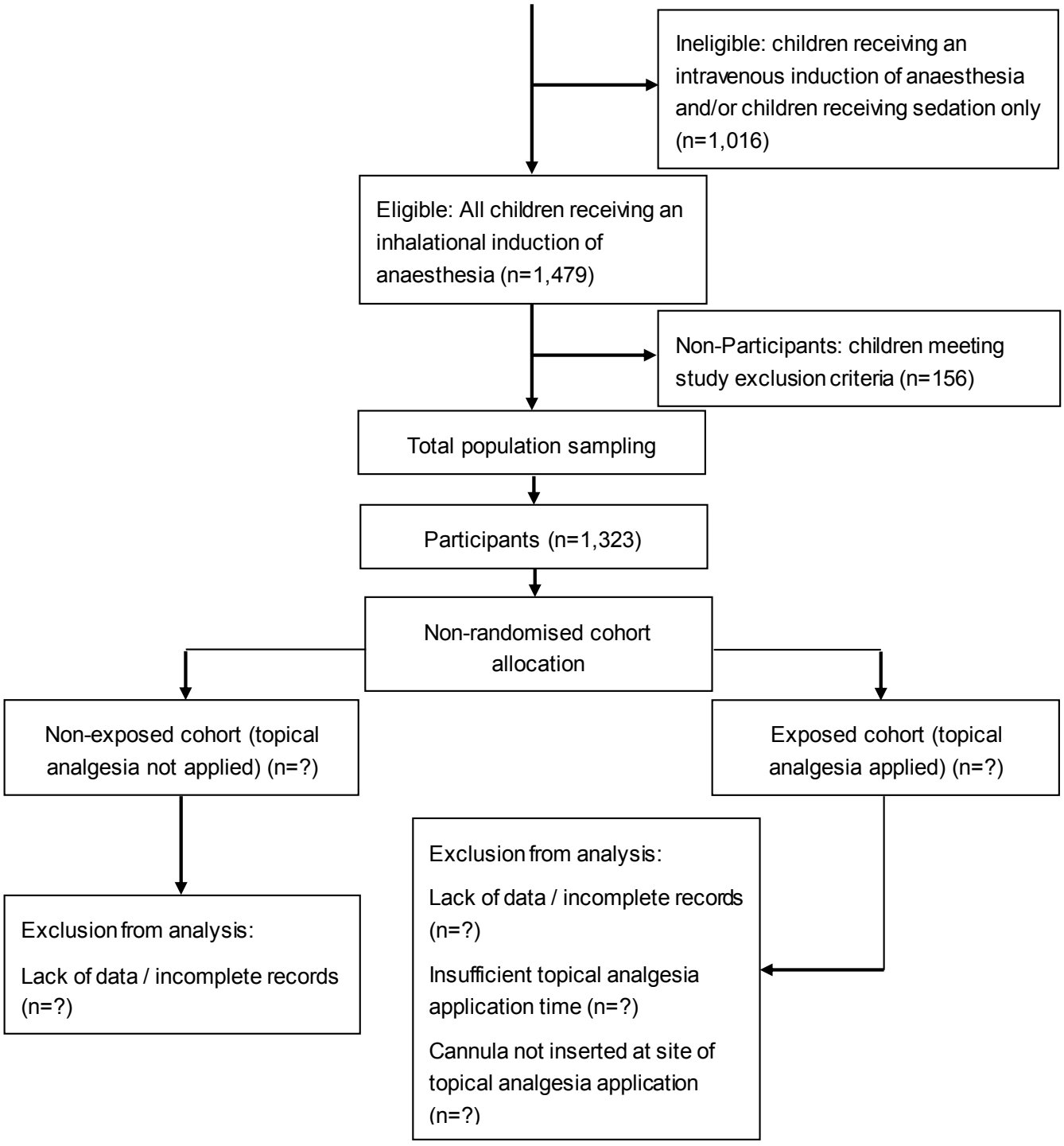
STUDY FLOW CHART

CONFIDENTIAL

Sampling frame: all NUH children receiving general anaesthesia in the defined study period (n=2,495)


Ineligible: children receiving an intravenous induction of anaesthesia and/or children receiving sedation only (n=1,016)
Eligible: All children receiving an inhalational induction of anaesthesia (n=1,479)
Non-Participants: children meeting study exclusion criteria (n=156)
Total population sampling
Participants (n=1,323)
Non-randomised cohort allocation
Non-exposed cohort (topical analgesia not applied) (n=?)
Exposed cohort (topical analgesia applied) (n=?)
Exclusion from analysis:
Lack of data / incomplete records (n=?)
Exclusion from analysis:
Lack of data / incomplete records (n=?)
Insufficient topical analgesia application time (n=?)
Cannula not inserted at site of topical analgesia application (n=?)

STUDY PROTOCOL

Topical Analgesia before Inhalational Anaesthesia: A Retrospective Observational Study

1. BACKGROUND

Many studies have identified painful procedures as one of the most feared and distressing components of medical care for children and their families, with fear of needle insertion remaining one of the most common childhood worries.[1-3]

Over the last decade, however, several bodies have published guidelines for management of acute pain, including procedural pain. The essential question now, is no longer whether children feel pain, but how best to treat and prevent it.[4]

Sadly, despite significant advances in pain management techniques, multiple studies and reviews continue to show that pain and distress remains poorly managed and that children, in particular, may still be suffering unnecessarily.[5]

Preventing pain is not only humane, but may also reduce the risk of subsequent morbidity, with the International Association for the Study of Pain (IASP) statement on "Why Children's Pain Matters" successfully enhancing practitioners' appreciation that children are a vulnerable segment of the population who deserve special consideration.[6]

One simple intervention that may be delivered prior to a needle insertion procedure, is the application of topical analgesia. Several topical analgesics are now available and have been found to be effective in several trials of non-anaesthetised children.[7-11] Yet the value of topical analgesia for children receiving an inhalational induction of anaesthesia remains undetermined.

2. RATIONALE

Cerebral cortical processing is a fundamental component of pain perception.[12] In non-verbal populations, measures of cortical activity may provide an insight into whether an individual is in pain, or in the case of the anaesthetised patient, whether the level of anaesthesia is sufficiently anti-nociceptive.

While many studies in animals,[13,14] adult patients[15-19] and anaesthetised children report an increase in electroencephalography (EEG) delta activity (with application of a topical analgesia diminishing the evoked increase in delta power caused by cannulation),[20] a smaller number of studies also report the opposite finding.[16,19,21,22]

Evidently, even with continuous EEG assessment, the assessment of analgesic adequacy in the anaesthetised patient, is problematic. In addition, EEG is rarely utilised in routine clinical anaesthetic practice, such that any conjecture regarding pain usually has to be inferred from limited surrogate markers such as spinal reflex withdrawal activity, resulting in patient movement.

In light of the observation that topical analgesia may diminish the evoked increase in delta power caused by cannulation,[20] any ability to reduce this more measurable surrogate marker, may further support the provision of topical analgesia for children receiving an inhalational induction of anaesthesia.

3. THEORETICAL FRAMEWORK

This study will be performed as a retrospective cohort observational study (a study which looks back in time, identifies cohorts (groups) of 'exposed' (those who received topical analgesia (skin numbing cream)) and 'non-exposed' (those who did not receive topical analgesia (skin numbing cream)) children and follows them over a period of time to see how their exposures affect their outcomes).

Since no studies have been conducted to date, to determine the value of topical analgesia (skin numbing cream) for children receiving an inhalational induction of anaesthesia (gas to go off to sleep), this has been designed as a non-randomised preparatory study. Being non-experimental in nature, this study will attempt to evaluate preliminary null hypotheses of association. Where association(s) and/or potential benefit(s) are observed to a statistically significant level, the value and feasibility of a future experimental study, in the form of a prospective randomised controlled trial, will be evaluated.

Through acting as a first step in exploring a novel intervention, this approach is felt to offer a safe and cost-effective indication of the value a future large-scale experimental trial, which in an uninvestigated field and with only a suggestible potential for benefit, would face numerous approval challenges.

4. RESEARCH QUESTION / AIM(S)

The primary aim of this study is as follows:

To determine whether topical analgesia (numbing skin cream) application prior to receiving inhalational induction of anaesthesia (gas to go off to sleep) may offer any beneficial effects for paediatric patients.

The primary outcome measure of interest is as follows: patient movement (as a surrogate marker of pain) during intravenous cannulation (insertion of a drip line into a vein).

The frequency of occurrence of the primary outcome measure will then be compared between those who received and did not receive topical analgesia (numbing skin cream) to test the primary 'preliminary null hypothesis of association' (default statistical belief): that the application of topical analgesia (skin numbing cream) prior to inhalational induction of anaesthesia (gas to go off to sleep) does not affect the frequency of patient movement during intravenous cannula insertion (insertion of drip line into a vein).

The secondary aim of this study is as follows:

To determine whether topical analgesia (numbing skin cream) application prior to receiving inhalational induction of anaesthesia (gas to go off to sleep) may offer any other beneficial effects for paediatric patients.

Secondary outcome measures will include: rate of successful initial venous cannulation (insertion of a drip line into a vein at first attempt), duration of the anaesthesia (as a surrogate marker of procedure time) and frequency of dermal (skin) reactions (itching, redness, blanching and swelling).

The frequency of occurrence or duration of each of the secondary outcomes measures will then be compared between those who received and did not receive topical analgesia (numbing skin cream) to test the secondary 'preliminary null hypothesis of association' (default statistical belief): that the application of topical analgesia (skin numbing cream) prior to inhalational induction of anaesthesia (gas to go off to sleep) does not affect the initial cannulation (first drip line insertion) success rate, time to secure the drip line or affect the frequency of dermal (skin) side effects.

Where association(s) and/or potential benefit(s) are observed, the value and feasibility of a future experimental study, in the form of a prospective randomised controlled trial, will be evaluated.

5. STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

This study will be performed as a retrospective cohort observational study (a study which looks back in time, identifies cohorts (groups) of 'exposed' (those who received topical analgesia (skin numbing cream)) and 'non-exposed' (those who did not receive topical analgesia (skin numbing cream)) children and follows them over a period of time to see how their exposures affect their outcomes).

Once HRA approval has been gained, it is planned that data collection and the subsequent analyses will proceed as follows:

Stage 1: 'Identification' (by a member of the usual care team)

All children from 1 month to 18 years of age undergoing elective or urgent inhalational induction of anaesthesia at Nottingham University Hospitals NHS Trust over a six month study period (August 2020 to January 2021) will be identified and considered eligible for inclusion.

Bluespier Theatre Management Systems at Nottingham University Hospitals NHS Trust (a secure pre-populated dataset) will be used for initial patient identification (all children receiving an inhalational induction of anaesthesia during the study period) and entered into an password protected Microsoft Excel file entitled the 'initial non-anonymised dataset' (using the unique Nottingham University Hospitals NHS Trust patient identification number - the only form of personal identifiable data to be recorded at any stage of the study). This will be performed by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust) and the dataset will be stored securely on an NHS Trust server following NHS Information Governance and data security policies and procedures.

Stage 2: Exclusion (by a member of the usual care team)

Children meeting the study exclusion criteria will be excluded at this stage by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

Exclusion criteria are as follows: children receiving an attempted awake venous cannula insertion and/or a failed intravenous induction of anaesthesia prior to an inhalational induction of anaesthesia, child or family history of malignant hyperthermia, congenital or idiopathic methaemoglobianaemia, glucose-6-phosphate dehydrogenase deficiency (G6PD), known sensitivity to topical analgesia and the use of analgesics within the preceding 24 hours.

All children meeting these exclusion criteria will be removed from the 'initial non-anonymised dataset' to create a 'non-anonymised participant dataset' (a password protected Microsoft Excel document which will be stored securely on an NHS Trust server following NHS Information Governance and data security policies and procedures).

Stage 3: 'Recruitment' (by a member of the usual care team)

The 'non-anonymised participant dataset' will contain all children who will become study participants (identified as being eligible and not meeting the study exclusion criteria). Using a total population (purposive) sampling technique, pre-existing information for all of these children (n=1,323) will be collected into a 'non-anonymised research dataset', which will be stored securely as a password protected Microsoft Excel document on an NHS Trust server following NHS Information Governance and data security policies and procedures, with subsequent data collection only completed for these sampled children. This will be performed by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

As such, only pre-existing child data will be collected (for children essentially being 'recruited' as units of observation) and no children will be actively 'recruited' as participants for interventional research purposes.

Stage 4: Data Collection (by a member of the usual care team)

Exposure status and outcome measures will be recorded for each 'recruited' unit of observation at this stage by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust) and incorporated into the 'non-anonymised research dataset'.

The unique Nottingham University Hospitals NHS Trust patient identification number (the only form of non-anonymised data to be recorded at any stage of the study) will be utilised for accessing the appropriate records, which will involve access to the Royal College of Anaesthesia logbook records (a mandatory and routine anaesthetic data collection process necessary for annual revalidation), Trust theatre records (Bluespier Theatre Management Systems at Nottingham University Hospitals NHS Trust), Perioperative care records, Trust medical records, Trust anaesthetic charts and Trust prescription charts.

At first, the exposure status will be established for each unit of observation (that is whether the individual child did or did not receive topical analgesia retrospectively). This will be an observational process according to events which have already occurred. Treatment allocation will not be influenced by this research project and a randomised interventional approach will not be implemented. The exposure status will be determined from the Royal College of Anaesthesia logbook 'note' section, where this information is routinely recorded. Trust prescription charts (electronically available through the Digital Health Record (DHR)) will always offer this information, however, should this not be immediately available to the usual care team member via the logbook.

The Royal College of Anaesthesia logbook will subsequently be accessed for each of the 'exposed' and 'non-exposed' units of observation and used to incorporate the following basic demographics into the

'non-anonymised research dataset': gender, age (date of birth will not be registered in order to maintain confidentiality), ASA grade (an identifier of patient wellbeing) and priority (elective or emergency procedure).

Further non-dependent information, including the grade of anaesthetist performing cannula insertion (Consultant or Trainee), history of prematurity (<38 weeks gestation) and child skin colour (light (Fitzpatrick scale I to IV) or dark (Fitzpatrick scale ≥ V)) will also be collected from the Royal College of Anaesthesia logbook, Trust anaesthetic charts and Trust medical records using the DHR.

Trust medical records and prescription charts will also be used to extract the required information to calculate body mass index (BMI) from data on height and weight, however, for children younger than 2 years of age, BMI is not applicable and therefore weight-to-age will be used. BMI and weight-to-age will then be converted to a z-score, with the use of age- and gender-specific growth charts from the Centers for Disease Control (CDC), to allow for comparison of patients of different ages.
For the recording of outcome status, all primary and a large proportion of secondary outcome measures are routinely recorded as an 'incident' or 'note' or in the case of procedure time as 'start-end' in the Royal College of Anaesthesia logbook but also in the Trust anaesthetic charts, Trust theatre records and Perioperative care records for all. These measures will be defined and recorded into the 'non-anonymised research dataset', as follows:

Occurrence of patient movement (as a surrogate marker of pain) during intravenous cannulation for those children receiving an inhalational induction. Movement will be defined as reflex hand and/or arm withdrawal and/or the initiation of excitatory movement(s) at the time of needle insertion.

Occurrence of dermal (skin) reactions at the site of topical analgesia application was assessed (inspection and verbal confirmation where possible) for erythema (redness) and oedema (swelling), blanching (pallor) and pruritis (itching) and where present, were documented by the healthcare provider.

Rate of FTSI (first time successful insertion) of cannula (with success defined as skin breached only once and the ability to freely instil 5 ml of normal saline intravenously (into the vein)).

For FTSI measurement, whilst the logbook may or may not offer this information, this will be always recorded in the Theatre records and Perioperative care records (with an 'X' marking a successful cannulation and an 'F' marking a failed cannulation in the perioperative are records skin check section). Where an F marking is registered, FTSI will be recorded as 'No'.

Although the 'duration of procedure', being defined as the time from first application of venous stasis to securing the intravenous cannula, would be the ideal indicator or the effect of topical analgesia on the temporal nature of cannulation, this information is not available for a vast majority of the units of observation. Instead, a proxy marker will to be used in this study: the 'overall anaesthetic time', which will always be available via the Logbook (Start – end time) and the Bluespier Theatre record ('Anaesthetic Start time to (arrival in) Theatre').

A summary of all the predictor (independent) and outcome (dependent) variables to be collected and where this information may be retrieved is summarised in the following Tables:

Predictor variable	**Measurement**	**Source of information**
Use of topical analgesia	Yes or No	RCoA Logbook (Notes) Trust prescription charts
Age	Years	RCoA Logbook
Gender	Male or Female	RCoA Logbook
Adiposity	BMI or weight-to-age z score	Trust prescription charts Medical records
Ethnicity / Skin colour	Light (Fitzpatrick scale I to IV) or Dark (Fitzpatrick scale ≥ V)	Trust medical records
History of prematurity (<38 weeks gestation)	Yes or No	Anaesthetic record Trust medical records
Grade of Anaesthetist performing cannulation	Consultant or non-Consultant	RCoA Logbook Anaesthetic record Theatre record (Bluespier) Perioperative care record
ASA	1, 2, 3, 4 or 5	RCoA Logbook
Priority	Elective or Urgent	RCoA Logbook

Outcome variable	**Measurement**	**Source of information**
Patient movement	Yes or No	RCoA Logbook

		(Incidents)
FTSI (first time successful insertion)	Yes or No	RCoA Logbook (Notes) Theatre record (Bluepsier) Perioperative care record (skin check section)
Skin side effects: Oedema Erythema Blanching Pruritis	 Yes or No Yes or No Yes or No Yes or No	RCoA Logbook (Incidents) Perioperative care record (skin check section)
Proxy-procedure time (overall anaesthetic time)	Minutes	RCoA Logbook (Start – end) Theatre record (Bluespier)

Evidently, a vast proportion of exposure and outcome measures may be evaluated via access to the mandatory Royal College of Anaesthesia logbook records, Trust anaesthetic charts, Trust theatre records, Trust medical records, Perioperative care records and Trust prescription charts, which will be available to a usual care team member (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

Where exposure and outcome variables are unavailable in the child's pre-existing data, these units of observation will be excluded from the analyses. In addition, all units of observation who received venous cannula insertion beyond the area of topical analgesia application and those who received topical analgesia less than 60 minutes prior to their inhalational induction of anaesthesia (considered insufficient topical analgesia application time) will also be excluded from the 'exposed' cohort during the analyses.

Stage 5: Anonymisation Process and Generation of Anonymised Research Dataset for Research Purposes (by a member of the usual care team)

Each unit of observation entered into the 'non-anonymised research dataset' will be allocated a Study ID (NOT0001 to NOT1323), alongside their Trust patient identification number. The Trust patient identification number will then be removed from the dataset at this stage, with the remaining information (including the Study ID) incorporated into an 'anonymised research dataset', by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

This 'anonymised research dataset' will be made available for research purposes in a password protected Microsoft Excel format (ready for conversion into an IBM SPSS format) and stored securely on an NHS Trust server following NHS Information Governance and data security policies and procedures.

Only one usual care team member (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust) will retain access to each of the non-anonymised datasets (in addition to the 'anonymised research dataset') and at no point will identifiable patient details be made available to any non-usual care team member.

Stage 6: Data Analysis

All statistical analyses will be performed using IBM SPSS Statistics Version 27.0 (Armonk, NY, USA) on an NHS Trust secure server following NHS Information Governance and data security policies and procedures. At this stage, the 'anonymised research dataset' (in Microsoft Excel format) will be converted into an IBM SPSS Version 27.0 dataset (the 'final anonymised research dataset'). No personal identifiable information will ever be utilised on the IBM SPSS platform. All of the analyses will be performed by the Chief Investigator (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

The baseline characteristics of those included will be summarised in terms of frequencies and percentages for categorical variables, with mean and standard deviation, or median and interquartile range (IQR), utilised for continuous variables, where appropriate.

With use of bivariate and multivariable analysis, the influence of all potential contributory factors for each outcome of interest will be examined. Where outcome information is unavailable, these units of observation (individual child data) will be excluded from the analyses.

For three of the outcome variables (patient movement, dermal side effects and FTSI), the crude (unadjusted) risk ratio and 95% confidence intervals (CI) will be measured for each of the categorical predictor variables (gender, skin colour, grade of anaesthetist inserting the cannula, priority, history of prematurity and application of topical analgesia) and the Mann Whitney U test will be calculated for each of the continuous predictor variables (age, BMI or weight-to-age z score). In addition, a Kaplan–Meier survival analysis, to compare the difference in mean anaesthesia time between curves will be performed (as a proxy marker of procedure time) for each cohort.

Multivariable binomial logistic binomial regression models (using all 'explanatory' baseline predictor variables) will subsequently be used to analyse the impact of topical analgesia exposure on frequency of movement and cannula FTSI (first time successful insertion) rates and a multivariable Cox regression analysis will be performed to analyse the impact of topical analgesia exposure on overall anaesthesia time.

From the models, adjusted odds ratios (AOR) or hazard ratios will be calculated, and model fit will be assessed by the Hosmer-Lemeshow test, *c* statistic, Nagelkerke's pseudo-R^2 and McFadden adjusted pseudo-R^2.

Within each of the multivariable analyses, statistical significance will be assessed at the 5% level based on a two tailed comparison.

6. STUDY SETTING

This is a single centre study which will be performed at Nottingham University Hospitals NHS Trust. The paediatric services at the Trust provide secondary and tertiary care for more than 450,000 children from Nottinghamshire and beyond.

7. SAMPLE AND RECRUITMENT

7.1. Eligibility Criteria

7.1.1. Inclusion criteria

Inclusion criteria include: data from all children from 1 month to 18 years of age undergoing elective or urgent inhalational induction of anaesthesia at Nottingham University Hospitals NHS Trust over a six month study period (August 2020 to January 2021).

7.1.2. Exclusion criteria

Exclusion criteria include: data from children receiving an attempted awake venous cannula insertion and/or a failed intravenous induction of anaesthesia prior to an inhalational induction of anaesthesia, child or family history of malignant hyperthermia, congenital or idiopathic methaemoglobinaemia, glucose-6-phosphate dehydrogenase deficiency (G6PD), known sensitivity to topical analgesia and the use of analgesics within the preceding 24 hours.

7.2. Sampling

7.2.1. Size of sample

Overall, all data from all children eligible for participation will be entered into the analyses. This will entail the recruitment of data from 1,323 children who have received an inhalational induction of anaesthesia and not met any of the study exclusion criteria. This sample size has been determined following the generation of preliminary dataset summaries, using the Bluespier Theatre Management System (without any requirement to access individual patient data), which has recorded 1,479 eligible children, with 156 children meeting the exclusion criteria, leaving 1,323 potential participants (units of observation) for whom further information may be collected from pre-existing data, once authorised.

Where formal hypothesis testing is performed, sample size calculations may be made using the following formulae:

Kelsey (Methods in Observational Epidemiology 2nd Edition, Table 12-15) and Fleiss (Statistical Methods for Rates and Proportions, formulas 3.18 &3.19)

Examination of previous audits suggest approximately 50% of children receive topical analgesia. Expecting an incidence of movement in non-exposed group of approximately 20% (Kong CF, Chew STH, Ip-Yam PC. Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. Br J Anaesth 2000;85:364-367 noted an incidence of 24%), study sample size calculations were performed as follows:

Sample Size: X-Sectional, Cohort, & Randomized Clinical Trials

Two-sided significance level (1-alpha): 95

Power (1-beta, % chance of detecting): 80

Ratio of sample size, Unexposed/Exposed: 1

Percent of Unexposed with Outcome: 20

Percent of Exposed with Outcome: 9.9

Odds Ratio: 0.44

Risk/Prevalence Ratio: 0.5

Risk/Prevalence difference: -10

	Kelsey	Fleiss	Fleiss with CC
Sample Size – Exposed	197	195	215
Sample Size – Non-exposed	197	195	215
Total sample size:	394	390	430

As such, a study sample size of 430 children would appear to give a power of >90% to detect a risk ratio of 0.5 at the 5% significance level.

Yet, this preparatory study has been designed to test a number of preliminary hypotheses, with a plethora of co-factors (predictor variables) and it has therefore been decided to use a larger sample size to ensure the study is sufficiently powered, with the recruitment of the data from all suitable children (n=1,323) across the six month study period.

7.2.2. Sampling technique

All children who may become units of observation (identified using the Bluespier Theatre Management Systems at Nottingham University Hospitals NHS Trust as being eligible and not meeting the study exclusion criteria) will be included into a Microsoft Excel document (the 'non-anonymised participant dataset'). Using a total population (purposive) sampling technique, pre-existing information for each of these units of observation (n=1,323) will be collected into a 'non-anonymised research dataset', which will be stored securely as a password protected Microsoft Excel document on an NHS Trust server following NHS Information Governance and data security policies and procedures, with subsequent information collection only completed from these sampled children's pre-existing data. This will be performed by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

7.3. Recruitment

7.3.1. Sample identification

Once HRA approval has been gained, it is planned that individual participants will be identified, screened for exclusion and 'recruited' as units of observation (with no active involvement of patients/service users as participants) into the study sample as follows:

Stage 1: 'Identification' (by a member of the usual care team)

All children from 1 month to 18 years of age undergoing elective or urgent inhalational induction of anaesthesia at Nottingham University Hospitals NHS Trust over a six month study period (August 2020 to January 2021) will be identified and considered eligible for inclusion.

Bluespier Theatre Management Systems at Nottingham University Hospitals NHS Trust (a secure pre-populated dataset) will be used for initial patient identification (all children receiving an inhalational induction of anaesthesia during the study period) and entered into an password protected Microsoft Excel file entitled the 'initial non-anonymised dataset' (using the unique Nottingham University Hospitals NHS Trust patient identification number - the only form of personal identifiable data to be recorded at any stage of the study). This will be performed by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust) and the dataset

will be stored securely on an NHS Trust server following NHS Information Governance and data security policies and procedures.

Stage 2: Exclusion (by a member of the usual care team)

Children meeting the study exclusion criteria will be excluded at this stage by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

Exclusion criteria are as follows: children receiving an attempted awake venous cannula insertion and/or a failed intravenous induction of anaesthesia prior to an inhalational induction of anaesthesia, child or family history of malignant hyperthermia, congenital or idiopathic methaemoglobianaemia, glucose-6-phosphate dehydrogenase deficiency (G6PD), known sensitivity to topical analgesia and the use of analgesics within the preceding 24 hours.

All children meeting these exclusion criteria will be removed from the 'initial non-anonymised dataset' to create a 'non-anonymised participant dataset' (a password protected Microsoft Excel document which will be stored securely on an NHS Trust server following NHS Information Governance and data security policies and procedures).

Stage 3: 'Recruitment' (by a member of the usual care team)

The 'non-anonymised participant dataset' will contain all children who will become study participants (identified as being eligible and not meeting the study exclusion criteria). Using a total population (purposive) sampling technique, pre-existing information for all of these children (n=1,323) will be collected into an 'non-anonymised research dataset', which will be stored securely as a password protected Microsoft Excel document on an NHS Trust server following NHS Information Governance and data security policies and procedures, with subsequent data collection only completed for these sampled children. This will be performed by a member of the usual care team (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust).

As such, only pre-existing child data will be collected (for children essentially being 'recruited' as units of observation) and no children will be actively 'recruited' as participants for interventional research purposes.

Of note, preliminary dataset summaries generated within the Bluespier Theatre Management System for each of the aforementioned three stages (without any requirement to access individual patient data), has recorded 1,479 eligible children, with 156 children meeting the exclusion criteria, leaving 1,323 potential participants for whom further information collection (from pre-existing data), once authorised and recruited (as units of observation), may proceed.

7.3.2. Consent

This study involves retrospective, observational, data collection and analysis from pre-existing clinical information by members of the usual care team. There is no active participation by children or their parents, no changes in treatment, or collection of new data. Furthermore, all data to be utilised for the purposes of research, will also be completely anonymised by a member of the usual care team, therefore we are requesting permission to waive the requirement to obtain written informed consent.

8. ETHICAL AND REGULATORY CONSIDERATIONS

No study related activities will begin until the study has Health Research Authority approval. The study will be conducted in line with the principles of International Conference on Harmonisation of Good Clinical Practice and the UK policy framework for health and social care research 2017. The study will be conducted under the supervision of the Sponsor and comply with requests for monitoring visits by appropriate regulatory authorities. Data collection, storage, access and retention will comply with GDPR 2018 and Data Protection Act 2018 requirements and all data will be anonymised for analysis.

8.1. Assessment and management of risk

This study is observational and considered to confer a low risk to participants. No active clinical interventions (with any potential to cause participant harm) will be introduced during this study.

8.2. Research Ethics Committee (REC) review & reports

This study involves retrospective, observational, data collection and analysis from pre-existing clinical information by members of the usual care team. There is no active participation by children or their

parents, no changes in treatment, no collection of new data and no identifiable information will be accessible to non-members of the usual care team, therefore we do not intend to seek REC approval.

Substantial amendments that require review by HRA will not be implemented until the HRA grants a favourable opinion for the study.

All correspondence with the HRA will be retained, with the Chief Investigator producing the annual report as required and notifying the HRA of the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the HRA, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the HRA.

8.3. Peer review

The peer review process has been instigated by the Chief Investigator (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust), who has obtained independent external peer review from the following individuals:

Christopher Tench (Senior Medical Statistician, Faculty of Medicine and Health Sciences, University of Nottingham)

Joyce Yeung (Associate Clinical Professor in Anaesthesia and Critical Care, University of Warwick)

In addition, support for this study has also been provided by the National Institute for Health Research (NIHR) Research Design Service (RDS) East Midlands group (with Dr. Doyo Enki as support advisor)

Furthermore, the study protocol has been internally reviewed and amended by a department / committee within the Chief Investigator's institution (the Nottingham University Hospitals NHS Research and Innovation department) and by Associate Clinical Professor Tim Card (Honorary Consultant Physician and Gastroenterologist at Nottingham University Hospitals NHS Trust, Member of Epidemiology Expert Review Panel for CRUK and Member of the International Editorial board for Alimentary Pharmacology and Therapeutics).

The peer review process for the study has been approved by the sponsor, who will continue to monitor conduct of the study against nationally agreed standards.

8.4. Patient & Public Involvement

Although regulatory guidelines from the Health Research Authority and Research Ethics Committee do not mandate patient consent for the completion of this study, patient and public involvement has and will continue to form a central part of the project.

This study has worked with several service users and the public by actively involving and engaging them in all parts of the research process as partners. This has been performed through consultation and collaboration with the Nottingham University Hospitals NHS Trust, Patient and Public Involvement and Engagement (PPI) department (Head of department: Kate Frost) and the NUH and NIHR GenerationR, Young Person Advisory Group (YPAG).

Through integrating PPI into our research process, it has been possible to formulate clear questions, processes and adjust the protocol to clarify and prioritise topics that are important for service users (including a focus on consent, our reasons for not requesting consent and the acceptability of our planned approach to the YPAG members).

A selection of replies from the YPAG are listed here:

"Yes, the summary uses appropriate language."

"I like the 'consent' paragraph with the 3 reasons. It makes it easier to read."

"Explanations of how they are going to use the data is good"

"I think it is okay to use data – I would want my data to be used to help other people"

"Overall, the summary is really good. It's easy to read and there isn't many pages to read from. I look forward to working with Matt and yourself in the new year."

Furthermore, through collaboration with the PPI, public interest may be satisfied and appreciation of our outcomes enhanced, through public dissemination of our findings beyond peer-reviewed publication. This will involve publication of our findings on the hospital website, informing the YPAG and supplying information in a patient group newsletter/website that are patient - and public centric rather than solely researcher-led.

8.5. Regulatory Compliance

Before any data is collected for the study, the Chief Investigator/Principal Investigator or designee will apply for HRA approval for the study and will make contact with the R&D department.

Prior to commencing recruitment, the local R&I team will confirm their capacity and capability to conduct the study, as per the HRA approval letter.

Any amendment to the protocol will be considered to potentially affect a site's capacity to continue in the study, the Chief Investigator/ Principal Investigator or designee will inform the Sponsor of the proposed amendment. The amendment will be submitted as per Section 8.7.

8.6. Protocol compliance

Protocol deviations, non-compliances, or breaches (recognised as departures from the approved protocol) will be documented and reported to the Chief Investigator and Sponsor immediately.

The research sponsor will ensure arrangements and systems are in place for the management and monitoring of research, taking a risk based approach. This study is observational and considered to confer a low risk to participants. The monitoring and auditing of the conduct of the study will reflect that set out in the UK Framework for Health and Social Care 2017 and Sponsor SOP RES-013 and SOP QMS-004.

8.7. Amendments

It will be the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the HRA. The sponsor will submit a valid notice of amendment for consideration. Site R&D departments will be provided with the information on the amendment. The level of review will be dictated by the category as assessed by the HRA (A, B or C).

8.8. Adverse Events

This study is retrospective and observational and so is considered to confer no risk to participants. No active clinical interventions are to be undertaken. The clinical safety profile of topical analgesia is now well established. The secondary outcomes of this study will observe the dermal side effects of topical analgesia use, but these are expected and will not constitute an adverse event although they will be documented in the study datasets and the Chief Investigator informed.

Of note, this research will not influence any of the anaesthetic practices offered to any of the children entered into the study. To this extent, provision of topical analgesia will be left solely to the discretion of the clinical team with no influence made by the research team (this is a non-randomised, non-interventional study design). Therefore, no active intervention is to be introduced in this study with the potential to result in an adverse event, however, through observation of negative clinical outcomes and amending practices (which will or will not have already occurred in the past) this study may promote patient safety (in the future).

8.9. Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the General Data Protection Regulation 2018 and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's/Act's core principles.

Sample (original) sources of information, including the pre-collected datasets (the RCoA Logbook and Bluespier records), alongside anaesthetic and surgical records and prescription charts, will remain as originally intended: as permanent, indelible records, without amendment by the research activity.

Overall 5 datasets will be generated during this study:

The 'initial non-anonymised dataset' (containing all eligible children)

The 'non-anonymised participant dataset' (containing children not meeting the exclusion criteria of the study)

The 'non-anonymised research dataset' (containing data from 1,323 children 'recruited' (as units of observation) from the 'non-anonymised participant dataset' using a consecutive sampling technique)

The 'anonymised research dataset' (the Microsoft Excel dataset containing the 1,323 recruited units of observation following data collection and anonymisation (removal of Trust patient identification number))

The 'final anonymised research dataset' (the IBM SPSS version of the 'anonymised research dataset', which will be used for data analysis)

Each of these datasets will be stored securely as a password protected documents (as Microsoft Excel or IBM SPSS formats) on an NHS Trust server following NHS Information Governance and data security policies and procedures.

Only the CI (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust), who is also a member of the usual care team, will have access to patients' personal data. The CI will also act as data custodian.

In compliance with the ICH/GCP guidelines, the Chief Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Investigator Site File, Sponsor Trial Master File and study documents shall be finally archived by the sponsor at secure archive facilities according to Sponsor SOP RES-028. This archive shall include a copy of each of the study datasets and associated meta-data encryption codes. Access to the data is by written request to the Sponsor.

8.10. Indemnity

As Nottingham University Hospitals NHS Trust is acting as sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

8.11. Access to the final study dataset

Two completely anonymised datasets generated by this study, essentially containing identical information, will be considered here as the 'final study dataset' (these being both the Microsoft Excel file: the 'anonymised research dataset' and the IBM SPSS adapted file: the 'final anonymised research dataset').

Each of these files will be stored securely as a password protected documents on an NHS Trust server following NHS Information Governance and data security policies and procedures.

Prior to the dissemination of the findings of the study, only the CI (M. Billingham, Department of Anaesthesia, Nottingham University Hospitals NHS Trust) and the Sponsor will have access to these files.

Following the dissemination of the findings of the study, only one of the completely anonymised participant level datasets (the 'anonymised research dataset'), will be made publicly available.

9. DISSEMINATION POLICY

9.1.Dissemination policy

This study will be registered on the ClinicalTrials.gov database. The study protocol, full study report, the anonymised participant level dataset (the 'anonymised research dataset'), and statistical code(s) for generating the results will be made publicly available after publication of the study.

No personal or patient identifiable data will be published and it is planned that the anonymised findings will be published via a peer-reviewed medical journal in the form of an original research paper.

In addition, following our collaboration with the Patient and Public Involvement and Engagement (PPI) department, the study findings will also be published on the hospital website, the Young Person Advisory Group (YPAG) will be notified and information will be supplied in a patient group newsletter/website that are patient - and public centric rather than solely researcher-led.

Although the supporting body will be acknowledged within the publication, none of the individuals offering support will have access to any of the datasets or possess publication rights. In addition, none of the data generated during the study will be used for secondary analyses.

9.2. Authorship eligibility guidelines and any intended use of professional writers

In line with the ICMJE (International Committee of Medical Journal Editors) recommendations, authorship will be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributors who meet fewer than all 4 of the above criteria for authorship will not be listed as authors, but will be acknowledged. Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading.

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11. APPENDICES

11.1. Appendix 1 – Schedule of Procedures

Procedures	Planned Time Schedule (2021)			
	May	May - June	June - July	August
Participant sampling (identification, exclusion and recruitment) (by usual care team member)	X			
Data Collection (by usual care team member)	X	X		
Creation of anonymised research datasets (by usual care team member)		X		
Statistical analysis (by CI)			X	
Dissemination of findings				X

11.2. Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	0.1	26/10/2020	M Billingham	Amendments in line with Trust R&I recommendations and PPI input
2	0.2	05/12/2020	M Billingham	Amendments in line with Trust R&I recommendations, NIHR RDS review, peer review