Short Title

Reducing fasting time for breast milk to 3 hours

Full Title

A prospective interventional study analysing gastric residual volumes in infants fed with breast milk 3 hours prior to general anaesthesia

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Funder (s):	Anaesthetic Department, King's College Hospital
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KEY WORDS

Fasting

Anaesthesia

Children

Breastfeeding

Gastric

LIST OF ABBREVIATIONS

AE	Adverse Event
CAG	Confidential Advisory Group
CI	Chief Investigator
CRF	Case Report Form
GE	Gastric emptying
GAfREC	Governance Arrangement for NHS Research Ethics
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form

PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
GRV	Gastric residual volume
TMF	Trial Master File

STUDY SUMMARY

STUDY OVERVIEW	
Full title	**A prospective interventional study analysing gastric residual volumes and young children fed with breast milk 3 hours prior to general anaesthesia**
Objectives	Measurement of volume of gastric contents for babies fed with breast milk 3 hours prior to general anaesthesia Correlation of gastric volume as estimated by ultrasound, with actual volume of gastric contents aspirated under anaesthesia Feasibility study for larger trial assessing gastric contents for babies fed formula milk 4 or 6 hours prior to general anaesthesia.
Type of trial	A prospective, interventional study of 60 term children aged 37 weeks to 18 months, undergoing elective surgery
Trial design and methods	The aim of this study is to ascertain the pH and Gastric residual volume (GRV) of gastric contents in 60 young children who are breast fed 3 hours prior to general anaesthesia. The secondary aim of this study is to ascertain how well ultrasound (USS) derived measurement of GRV, using the gastric antrum cross sectional area (ACSA), correlates to direct measurement via aspiration. Findings of this study will inform the design of a larger randomised controlled trial assessing GRV in infants fed 4 or 6 hours prior to general anaesthesia. Following Research Ethical Committee approval and registration on clinicaltrials.gov, recruitment is estimated to begin in September 2022. We will perform a prospective, interventional study of 60 term young children aged 37 weeks post menstrual age to 18 months, undergoing elective surgery at Kings' College Hospital and Birmingham Women and Childrens' Hospital. Parents who have provided consent to participate will be asked to begin their final breast feed 3 hours prior to anticipated procedure time. Parents will be asked to feed as normal until satiety, and record start and finish times. Parents using expressed breast milk (EBM) will be included, and given the same instructions. They will also be asked to note down the volume of EBM given. Prior to anaesthesia, a gastric ultrasound (USS) will be performed in the lateral decubitus position, and gastric antrum cross sectional area (ACSA) will be recorded. Once asleep and following securement of the airway, an orogastric tube will be inserted into the stomach. Any gastric contents will be aspirated and volume will be recorded. In the event that a child becomes distressed during the USS examination, the study investigator may defer completion of the scan until after induction of general anaesthesia.
Health condition(s) or problem(s) studied	Gastric emptying in term young children undergoing elective surgery
Target sample size	60
Trial duration per participant:	24 hours

Main inclusion/exclusion criteria:	Inclusion criteria Babies born after 37 weeks post menstrual age, and upto 18 months of age Babies born prior to 37 weeks gestation, who are now greater than 37 weeks corrected post menstrual age Elective surgery Exclusion criteria Previous surgery to stomach or upper gastrointestinal tract Liver, heart or kidney diseases Diabetes Being born prior to 37 weeks gestation who are now greater than 37 weeks post menstrual age, but with significant lung, cardiac or neurological comorbidity. Severe lung diseases that mean they use oxygen or a ventilator at home Previous involvement in this research study, less than 28 days prior.
Statistical methodology and analysis:	Categorical variables will be analysed by Chi-squared or Fisher's exact test as appropriate. Continuous variables will be tested for normality of distribution then analysed by t-test or Mann Whitney U test as appropriate. The sample size of 60 would allow the estimation of a recruitment rate of 60%, within a 95% confidence interval of +/-10%.
STUDY TIMELINES	
Study Duration/length	2 years
Expected Start Date	September 2022
End of Study definition and anticipated date	End of recruitment, anticipated to be September 2024
Key Study milestones	Submission to REC May 2022 Preparation of CRF and training for PIs and study team July-August 2022 First patient recruitment September 2022 at KCH First patient recruitment November 2023 at BWC
STORAGE of SAMPLES (if applicable)	
Human tissue samples	N/A
Data collected / Storage	Any gastric contents aspirated from a participant will be measured for volume and then disposed of immediately.

1 INTRODUCTION

The detrimental effects of prolonged fasting in young children prior to general anaesthesia (GA) are well known, and include thirst and dehydration, hunger, low blood sugar and acidosis at induction of anaesthesia.

The aim of this study is to ascertain the gastric residual volume (GRV) of gastric contents in 100 infants who are breast fed 3 hours prior to general anaesthesia. The secondary aim of this study is to ascertain how well ultrasound (USS) derived measurement of GRV, using the gastric antrum cross sectional area (ACSA), correlates to direct measurement via aspiration.

It is anticipated that demonstrating that there is minimal gastric residual volume after a 3 hour fast will add to a body of evidence in support of reducing fasting times for breast feeding in children.

BACKGROUND AND RATIONALE

Current UK guidance recommends a fasting time of 4 hours for breast milk prior to general anaesthesia. European guidance has recently changed, advocating a 3 hour fast for breast milk. Some tertiary centres in the UK have already adopted this change,

Gastric emptying (GE) of breast milk and formula preparations has been extensively studied in neonatal intensive care settings for preterm and low birth weight infants, in order to establish optimum feeding regimens for growth. Breast milk has been demonstrated to empty from the stomach in an exponential manner, with gastric ultrasound studies illustrating that antrum measurements return to baseline (pre feed measurements) within 3 hours. Methodologies utilised in such studies can make applying findings to current routine anaesthetic practice difficult: Such as inclusion of very low birth weight infants, use of fortified breast milk, administering feeds via nasogastric tube, and using gastric ultrasound to estimate GRV, rather than direct measurement of volume, for example by naso-gastric tube, Animal studies have illustrated that severe lung injury occurs when volumes of acidified milk above 0.8ml/kg are instilled into the trachea.

There is a paucity of evidence in breast fed, un-premedicated term babies/infants subjected to a 3 hour fast prior to GA, where GRV is measured directly.

Pulmonary aspiration is known to be a rare event associated with lower morbidity and mortality in children than in adults . In animal studies, instillation of acidic solutions at pH1 are associated with increasing severity of lung injury as volume of solution increases above 0.8ml/kg of pH 1. A small single centre study conducted in Australia in 30 premature babies reported GRV following 3 hourly nasogastric tube feeds of breast milk. 83% of babies had an empty stomach at 3 hours, and of those with some milk left behind, the mean GRV was 0.4ml/kg. a child or adult with a full stomach is more hazardous and requires alteration of the anaesthetic technique to minimise risk of aspiration. Gastric ultrasound (USS) is a useful tool for assessing stomach volume prior to induction of anaesthesia. Various formulae have been devised to convert measured gastric antral area to predicted gastric residual volume in children. USS is validated in older children and adults in measurement of gastric ACSA and derived volume of gastric contents. To date there is no 'safe cut off' value for residual

volume of breast milk in babies, prior to anaesthesia. For fasted adults, where any residual volume is likely to be acidic clear fluid, a volume of 1.5ml/kg has been advocated. A much lower value of 0.8ml/kg has been advocated in this study, based on evidence from animal studies, the main difference being that partially digested milk in the stomach will be particulate in nature. If the predicted volume on ultrasound is greater than this, surgery will be deferred, cancelled, or a modified anaesthetic technique used.

2 OBJECTIVES

2.1 Primary Objective

The primary aim of this study is to ascertain the GRV of gastric contents in 100 infants who are breast fed 3 hours prior to general anaesthesia.

2.2 Secondary Objectives

The secondary aim of this study is to ascertain how well ultrasound (USS) derived measurement of GRV, using the gastric antrum cross sectional area (ACSA), correlates to direct measurement via aspiration.

2.3 Tertiary Objectives

The final objective of this study is to inform the design of a larger randomised controlled trial assessing GRV in infants who are formula fed, either 4 or 6 hours prior to a feed. This study will be hosted by King's College Hospital, and will use similar methodology to screen and recruit patients.

3 STUDY DESIGN

- We will perform a prospective, interventional study of 60 term children aged 37 weeks PMA to 18 months, undergoing elective surgery at KCH and BWC. A minimum sample size of 35 was calculated for a non-inferiority margin of 0.2 ml/kg, based upon a standard deviation of 0.76 ml/kg for gastric residual volume with 90% power and a significance level of 0.05. A sample size of 30.9 was calculated to be necessary. This was increased to 35 to allow for a 10% dropout rate. Calculations were performed in the TrialSize package in R. Expanding the sample size to 60 at two NHS sites will increase the impact of our findings and will be adequate to inform the larger study in terms of recruitment rate .
- Approximate duration of enrolment is 2 years.
- Categorical variables will be analysed by Chi-squared or Fisher's exact test as appropriate. Continuous variables will be tested for normality of distribution then analysed by t-test or Mann Whitney U test as appropriate.

4 STUDY SCHEDULE

All children are routinely assessed in a virtual or face to face clinic prior to planned surgery (so called pre-assessment). This assessment is carried out by a consultant anaesthetist or nurse. As part of the pre-assessment process, parents are asked if they would be willing to be contacted about research projects. If confirmed, the study team will contact the parent/guardian prior to the planned surgery date to discuss eligibility and give information about the study.

The consent process will take place either around the time of pre-assessment verbally over video link or telephone, and confirmed with written consent on the day of surgery or for in-patients, the day before surgery. For those who have consented to take part, the study team will confirm eligibility as necessary using the child's electronic patient record.

Following recruitment, all children will be followed up for the first 24 hours following the intervention. Any adverse events will be recorded. Participants may withdraw from the study at any time. Parents will be kept informed of any relevant events or findings occurring from admission to the ward through to discharge home that are felt to be relevant to the study.

The study enrolment will cease when the 100 children have been recruited. The study will be terminated prematurely if there is any unexpected serious adverse event

Table 1: Schedule of Assessments

	Pre assessment	**Pre operative visit**	**Anaesthetic room**	**Operating theatre**	**Post operative visit**
Visit No	**1**	**2**	**3**	**4**	**5**
Window of flexibility for timing of visits:	e.g +/- 2 weeks	1 hour	20 minutes	5 minutes	24 hours
Informed Consent	X (verbal)	X (written)			
Medical History	x				
Physical Examination					X if applicable
Vital Signs		x			X if applicable
Eligibility confirmation		x			
Trial specific interventions Routine interventions			USS examination Routine checks as per WHO checklist	GRV of gastric contents USS examination under general anaesthesia, if not completed awake General anaesthesia Surgery	

Adverse Events Review				x	x
Concomitant Medication Review (if applicable)	x	x			

5 CONSENT

Eligible participants will be identified at the time of the pre-assessment clinic (usually a virtual meeting between a consultant anaesthetist or nurse and the parent/guardian of a child, upto 4 weeks prior to surgery). During this process all patients and parents are asked if they consent to being contacted for research purposes.

Parents/guardians who give consent to being approached by the study team at the time of pre assessment, will be contacted within the 4 weeks prior to planned surgery to discuss eligibility and receive information regarding the study.

The consent process will take place either around the time of pre-assessment verbally over video link or telephone, and confirmed with written consent on the day of surgery, or for in-patients on the day before surgery.

Non English speakers will not be eligible for inclusion. As the study population are children upto 1 year of age, the consent process will involve communication with parents/guardians only.

6 ELIGIBILITY CRITERIA

Inclusion Criteria

Babies born after 37 weeks post menstrual age, and upto 18 months of age

Babies born prior to 37 weeks gestation, who are now greater than 37 weeks post-menstrual age on the day of surgery

Elective surgery

Exclusion Criteria

ASA score of 4 or above (American Society of Anaesthesiologists' physical status classification system)
Emergency surgery

Known or suspected gastro-intestinal disease or hepato-biliary disease including varices and strictures within the upper gastro-intestinal tract

Gastro-oesophageal reflux disease (GORD): either on treatment or under investigation),

liver or renal failure,

oesophageal achalasia,

diabetes mellitus with gastroparesis,

Previous surgery which may alter gastric emptying or anatomy of oesophagus, stomach or small intestine
Anticipated difficult airway

Concomitant administration of any other medication orally prior to anaesthesia, but excluding sedative pre-medication eg midazolam

Bleeding disorder

Prematurity (defined as a child born earlier than 37 weeks gestation, who is less than 37 weeks post menstrual age on the day of surgery)

Chronic lung disease requiring home oxygen or any form of non-invasive ventilation, including optiflow.

Patients taking antacids or pro-kinetic drugs, or requiring them pre-operatively

Patients taking immunosuppressive medication

Children or household members with symptoms suggestive of current or recent SARS-Cov-2 (covid 19) infection

Children or household members with a recent RT-PCR positive swab result for SARS-Cov-2

Children under 60 weeks corrected gestational age whose mother had a RT-PCR positive swab in the third trimester of pregnancy

Children already recruited into this research study within the last 28 days.

7 PATIENT AND PUBLIC INVOLVEMENT (PPI)

We are planning to interview 20 sets of parents who are currently breast feeding their children. We will use this opportunity to check instructions we give to recruited families are clear, easy to understand and realistic to achieve.

8 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the KCH R&I Office, and deemed sufficient to cover the requirements of the study. The study will be reviewed by R&I at BWC and the same process will be followed there.

This study does not require any external funding. All equipment to be used is available for routine care of children undergoing general anaesthesia. We have confirmation from the Clinical Director for Anaesthetics and Theatres at KCH and BWC, that any small costs (estimated upto £160) incurred for consumables, will be covered by the department.

DATA HANDLING AND MANAGEMENT

Paper consent sheets and CRFs will be pseudonymised and held in a locked office within the anaesthetics department. Electronic data will also be pseudonymised prior to storage on the CI's password protected Trust computer. Statistical analysis will be performed by Dr Nielsen, a Consultant Anaesthetist at Cambridge University Hospitals NHS Trust. Only this pseudonymised data will be shared with Dr Nielsen via nhs mail.

9 MATERIAL/SAMPLE STORAGE

Any gastric fluid aspirated from a patient will be measured for volume and acidity and then immediately disposed of.

10 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by KCH R&I.

This study has been peer reviewed within KCH by an independent and relevant peer review committee on 23rd March 2022. The Sponsor has accepted these reviews as adequate evidence of peer review. The study has been reviewed by R&D at BWC and confirmation obtained that BWC has the capacity and capability to deliver the study.

The study was deemed to require regulatory approval from the following bodies (list). Each approval will be obtained before the study commences.

- HRA
- REC

11 ADVERSE EVENTS AND INCIDENT REPORTING

11.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the intervention/treatment/procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: ● results in death, ● is life-threatening*, ● requires hospitalisation or prolongation of existing hospitalisation**, ● results in persistent or significant disability or incapacity, or ● consists of a congenital anomaly or birth defect

*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.

16.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

Severity

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).

Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

Expectedness

Category	Definition
Expected	An adverse event which is consistent with the available information about the intervention/treatment/procedure in use in this study.
Unexpected	An adverse event which is not consistent with the available information about the intervention/treatment/procedure in use in this study*

* this includes listed events that are more frequently reported or more severe than previously reported

16.3 Procedures for recording adverse events

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

16.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF.

All SAEs will also be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an SAE form and the form will be emailed to the R&I Office (kch-tr.researchqualityassurance@nhs.net) within 1 working day of becoming aware of the event.

Where the event is unexpected and thought to be related to the intervention/treatment/procedure this will be reported by the Investigator to the REC and Health Research Authority, using the SAE Report form for non-CTIMPs (available from the HRA website) within 15 days.

Premature termination of the study

The study may be prematurely discontinued by the Sponsor, CI or HRA on the basis of new safety information, for example if the participants have a statistically significant increased incidence of serious adverse events compared with published literature, or if the study team were to have other safety concerns at any time. IF the trial is discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and REC will be informed within 15 days of the early termination of the study.

16.6 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC, Health Research Authority and R&I office of the measures taken and the circumstances giving rise to those measures.

16.5 Protocol deviations and notification of protocol violations

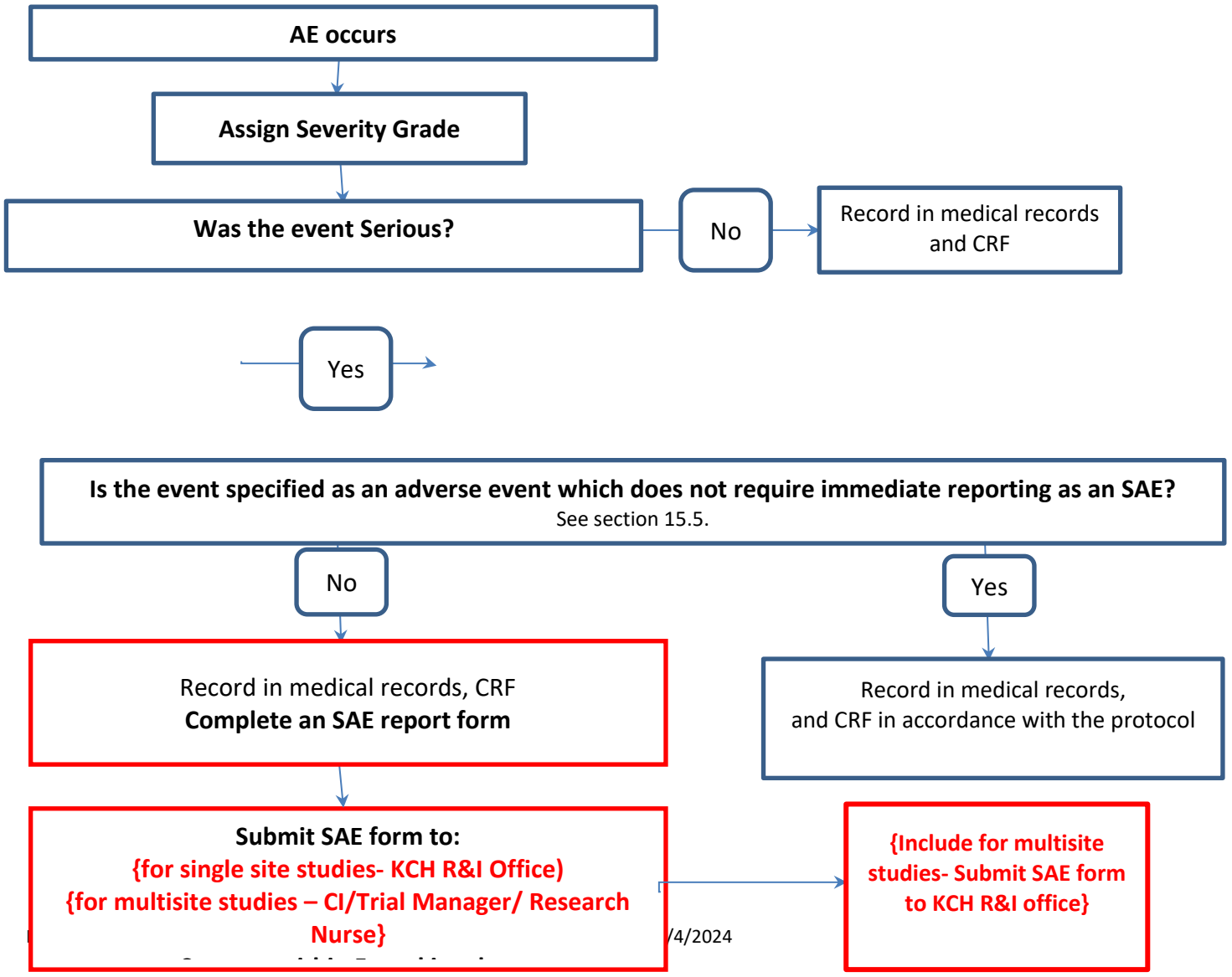
A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study.

The CI and R&I Office should be notified immediately of any case where the above definition applies during the study conduct phase.

Flow Chart for SAE reporting



/4/2024

16.6 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

17 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

18 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

All members of the study team will have a recent (within 2 years) certificate for completion of the Good Clinical Practice course. All team members are employed as substantive consultants or registrars in training posts in anaesthesia at KCH. All team members will be trained in using the CRF, pH meter and performance of gastric USS, and will have received mandatory Trust training in data protection and GDPR .

INTELLECTUAL PROPERTYINDEMNITY ARRANGEMENTS

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The

Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office

19 ARCHIVING

Pseudonymised data will be archived for 25 years: Paper CRFs will be stored in a locked office within the anaesthetic department and electronic data will be stored on the CI's password protected Trust PC.

20 PUBLICATION AND DISSEMINATION POLICY

Findings of the study will be submitted for publication in a relevant peer reviewed scientific journal. Findings may also be shared at a relevant national or international conference.

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