Non-CTIMP Study Protocol

*COVID Cleft*

Impact of the COVID pandemic on Cleft surgery

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LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| **ACCORD** | Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board |
| **CI** | Chief Investigator |
| **CRF** | Case Report Form |
| **GCP** | Good Clinical Practice |
| **ICH** | International Conference on Harmonisation |
| **PI** | Principal Investigator |
| **QA** | Quality Assurance |
| **REC** | Research Ethics Committee |
| **SOP** | Standard Operating Procedure |
| **CLP** | Cleft lip and palate |
| **CL+/-P** | Cleft lip with or without cleft palate |
| **UCLP** | Unilateral cleft lip and palate |
| **BCLP** | Bilateral cleft lip and palate |
| **CP** | Cleft palate |
| **RS** | Robin sequence |
| **LAHSHAL** | LAHSHAL classification system for cleft lip and palate |
| **VPI** | Velopharyngeal Incompetence |
| **CFSGBI** | Craniofacial Society of Great Britain and Ireland |
| **Cleft CSG** | NIHR UK and Ireland Cleft and Craniofacial Clinical Studies Group |
| **ECTU** | Edinburgh Clinical Trials Unit |
| **REDCap** | Research Electronic Data Capture |

# INTRODUCTION

## BACKGROUND

Cleft lip and/or palate is the commonest craniofacial anomaly and occurs in 1 in 650 to 700 live births (1). Timing of surgery to repair the original cleft as well as any follow up surgery is an important variable in quality of care and outcome, with potential to adversely impact on children’s speech, hearing, development, confidence, appearance and oral health. This led to all UK cleft centres agreeing quality standards (2) for timing of cleft surgery, as described in the Cleft Quality Dashboard and endorsed by the Craniofacial Society of Great Britain and Ireland (CFSGBI). Despite these accepted standards in the UK, some disagreement exists on the optimum timing of primary surgery particularly cleft palate (CP) repair

However, all cleft surgery (other than airway interventions) is elective and as a result, cleft surgery has been postponed during the COVID pandemic, with some centres only now resuming cleft surgery. Thus, there will be a delay in carrying out procedures, far greater than would normally be the case, as well as the ongoing impact of the existing backlog.

There are increasing reports of the impact of COVID on adults undergoing surgery, but relatively little data on babies and children who need to undergo elective surgery. COVID appears to affect fewer children than adults; and literature on COVID in babies and children is relatively sparse. However, reports of a Kawasaki like inflammatory condition (3)demonstrates that children can be severely affected by COVID, which underlines the importance of studies focussed on children, particularly to inform decision making around the safest timing for elective surgery.

Additionally, surgeons normally carry out cleft surgery using one or more combinations of the following equipment – headlights, magnifying loupes, operating microscope. Wearing PPE interferes with this equipment and also introduces problems of its own, particularly during long operations. Cleft surgeons spend a longer period of time close to the faces of anaesthetised patients and are exposed to any leaks around the endotracheal tubes for a greater duration than any other member of theatre staff.

## RATIONALE FOR STUDY

This study aims to determine the impact of COVID on cleft surgery. This the first time in the UK that a large cohort of patients will be undergoing cleft surgery with such large delays in timing of surgery. Additionally, we do not know how the prevalence of COVID in the community and possibly in patients will affect the postoperative course of children undergoing surgery, particularly in the case of babies and procedures that may bring about a temporary reduction in airway volume. Given the relative rarity of COVID in babies and children, it is particularly important that we share data across the UK following the resumption of cleft surgery. This will enable better understanding of perioperative safety and outcomes. Additionally it will provide data to guide practice, in particular the need to suspend/delay elective surgery during further waves of this pandemic.

This is also an opportunity to study the impact of delays to planned cleft surgery, in a large cohort and identify any impact on outcomes that may be related to such delays.

This study will also examine cleft surgeons experiences of wearing PPE with loupes, headlights or the operating microscope and will study solutions that may prove useful in similar situations. PPE is particularly relevant for cleft surgery, because the surgeons face is close to the patients mouth and the endotracheal tube (ET) for a considerable duration. Cleft surgery requires a Rae tube, curved to lie flat on a patient’s chin. Not all units in the UK had access to cuffed Rae tubes in small sizes and this practice has been changing. Our study will report on these changes.

# STUDY OBJECTIVES

## OBJECTIVES

### Primary Objective

Determine the impact of the COVID pandemic, on elective cleft surgery timings and outcomes.

### Secondary Objectives

Study individual units screening processes, screening outcomes and their impact on clinical decision making regarding timing of surgery

Determine prevalence of COVID positive tests in infants (+Parents where testing is is done as part of unit protocols)

Incidence of postoperative complications

Impact on patient follow up (remote or in person)

Duration to return to usual protocol timelines

Surgeons’ reports of challenges of wearing PPE and operating with loupes/headlight/microscope

## ENDPOINTS

### Primary Endpoint

Point at which patients are able to have surgery in keeping with UK standards and unit protocols, in terms of timing of surgery.

# STUDY DESIGN

Study type: Observational

Setting: Tertiary cleft centres. All 11 cleft units (16 cleft surgical sites) in the UK will be approached for participation. This will include cleft surgery consultants and trainees. There is an well established network and history of multicentre collaborative studies across the 11 UK cleft centres.

Study Duration – until UK Cleft surgery has caught up with the COVID backlog.

Follow up duration – 3-4 months, until patients have had at least one post-op review.

Outcomes – as summarised above, in box 3

# STUDY POPULATION

## INCLUSION CRITERIA

All patients undergoing primary or secondary cleft surgery, including submucous cleft palate repair and non-cleft VPI surgery, under the age of 16 years.

## EXCLUSION CRITERIA

Patients 16 years and older

## CO-ENROLMENT

This study is a non-interventional study and only involves submission of anonymised data about ongoing treatment. Patients about whom data are submitted to this study may also be (or have been) enrolled in the ongoing UK Cleft Collective Birth Cohort study. This is a non-interventional cohort study.

# PARTICIPANT SELECTION AND ENROLMENT

## IDENTIFYING PARTICIPANTS

**Study design:** a multicentre, UK observational study

**Study setting:** Surgical sites of nationally designated Cleft Centres

**Inclusion criteria:** any patient under the age of 16yrs, undergoing primary or secondary cleft surgery under a general anaesthetic

**Exclusion criteria:** as an observational study, this is an audit of all cleft surgery so there are no exclusions other than patients 16 years and older.

## CONSENTING PARTICIPANTS

This is exclusively an observational study. Participants will continue to receive treatment in keeping with each cleft centre’s protocol. Studies will be registered at participating sites as an audit and therefore no patient / parent consent will be specifically sought. However, the findings from the study will be shared with patients, parents and carers using established networks and processes for public involvement with cleft research.

# STUDY ASSESSMENTS

## STUDY ASSESSMENTS

The only assessments and interventions that will be performed are those that form part of each centre’s routine cleft treatment protocol. No additional assessments or interventions will be performed for the purpose of this study.

## LONG TERM FOLLOW UP ASSESSMENTS

Following discharge from hospital, patients will be reviewed in keeping with the unit protocols, taking into account any relevant changes due to COVID-19.

Data from follow up assessment findings will be submitted upto a period of 4 months postoperatively.

## STORAGE AND ANALYSIS OF SAMPLES

Not applicable

# DATA COLLECTION

Data to be collected, as well as time points, are included in Appendix A

Data will be submitted by the operating surgeon or by a member of their team

Sites will be contacted through the UK/Ireland Cleft Surgeons’ Clinical Excellence Network (CEN) and the Cleft Multidisciplinary Trainee Collaborative. If needed, sites will be sent email reminders or will be phoned.

## Source Data Documentation

Source documents include medical notes (paper/electronic), nursing notes,

## Case Report Forms

Data will be uploaded by centres using a REDCap database built for this project.

# DATA MANAGEMENT

### Personal Data

### The following personal data will be collected as part of the research:

### Date of birth, sex, diagnosis, ethnicity, postcode,

### Personal data will be stored by the research team at ECTU. The CI will have access to personal data and the code break / key will be kept according to ECTU protocols.

### Data Information Flow

Local clinicians will be given access to a REDCap database to enter study data. Some data may need to be entered retrospectively from the patients’ notes, depending on the date of site opening, access to REDCap and the data units re-commenced elective cleft surgery.

### Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

### Data Controller

The University of Edinburgh is the data controller.

### Data Breaches

Any data breaches will be reported to the University of Edinburgh Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

# STATISTICS AND DATA ANALYSIS

## SAMPLE SIZE CALCULATION

Observational study, with the aim of including all babies and children undergoing cleft surgery in the UK and Ireland after the resumption of elective cleft surgery.

## PROPOSED ANALYSES

Variables to be analysed are included in Appendix A. A statistical analysis plan will be written to analyse primary and secondary outcmes.

# ADVERSE EVENTS

# This is an observational study. Any complications will be dealt with in accordance with clinical protocols at the local unit.

# OVERSIGHT ARRANGEMENTS

This study will follow a similar approach to an existing similar study, The HAREM Study (Had Appendicitis and Resolved/Recurred Emergency Morbidity/Mortality). The following has been quoted from the HAREM protocol.

**Local approvals:** The Centre lead at each participating site is responsible for all members of their team have up to date GCP training and will have local responsibility for data quality and entry. They will obtain necessary local approvals in line with their hospital’s regulations and will be required to confirm that a local approval is in place at the time of uploading each patient record to the study database. REDcap accounts will not be issued until evidence is provided via hospital local leads that the following approvals are in place at each centre:

1. Successful registration of COVID Cleft at the hospital site
2. Caldicott Guardian permission for data to be submitted to REDcap

Centre leads should discuss with their head of research whether it is possible to expedite the approvals process in view of the urgency of global pandemic. It should be highlighted that this is an investigator-led, non-commercial, observational (no changes to normal patient care) study with only routinely available non-identifiable data will being collected. The project can be registered as either a service evaluation or clinical audit.

Prior to formal local study approval, if permitted, collaborators may prospectively collect data on hard copy case report forms, but this should not be uploaded to the REDCap database until approval is confirmed.

# GOOD CLINICAL PRACTICE

## ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

## Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

## INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

*Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.*

### Informed Consent

This is an observational audit and we will not be seeking consent from patients who will continue to receive treatment in keeping with local unit protocols.

### Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator’s responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

### Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

### GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor.  GCP training status for all investigators should be indicated in their respective CVs.

### Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

### Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place

# STUDY CONDUCT RESPONSIBILITIES

## PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

## STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

## END OF STUDY

The end of study is defined as the last participant’s last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

## CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Treatment will be continued according to local unit protocols

## INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

* The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
* Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
* Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

# REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

## AUTHORSHIP POLICY

**Authorship**: Individual centre collaborators and data validators will be eligible for PubMed-citable co-authorship as collaborators, as long as they return a validated dataset by the closing date of the project. It is upto local teams to decide upon the number of collaborators for their team and to select one as a data validator. Centres with >5% missing data will be excluded from the analysis and the contributing local team removed from the authorship list. An example of this approach to multiple authorship can be found at: <https://www.ncbi.nlm.nih.gov/pubmed/31188201>.

**Publication/presentation:** Data will be reported as a whole cohort and submitted to relevant journals. The project will be submitted for presentation at national and international conferences.

# Appendix A

|  |  |
| --- | --- |
| Study ID |   |
| Date of Birth | dd/MM/YYYY |
| Premature | Yes (if yes, enter Estimated Due Date) No |
| Sex |  Male Female |
| Ethnicity | standard dropdown list |
| Diagnosis | LAHSHAL code |
| Diagnosis SMCP | Yes No |
| previous surgical history | consider free text |
| Syndrome | Yes (if yes, free text for syndrome) No |
| Associated Conditions | Yes (if yes, free text) No |
| Weight at surgery in grammes |   |
| Feeding (select one or more) | breast, bottle, tube fed, weaned yes |
| Weaned | Yes No |
| Operation (select one or more) | Unilateral Cleft lip repair |
| Unilateral Cleft Nose repair |
| Bilateral Cleft lip repair |
| Bilateral Cleft Nose repair |
| Cleft palate repair |
| Vomerine flap(s) (as part of lip repair) |
| ABG |
| fistula repair |
| grommet insertion |
| VPI surgery |
| Associated Conditions | Yes (if yes, free text for conditions) No |
| Robin Sequence | Yes No NA |
| Cleft Centre | free text / use centre code |
| Operating surgeon | free text / use surgeon code |
| ASA |  I II III IV V |
| Date of preop assessment |  DD/MM/YYYY  |
| Preoperative COVID swab(s) on patient (select one or more) | 2 weeks preoperative |
| 48 hrs preoperative |
| Other 1 |
| Other 2 |
| Patient's COVID swab test | Positive/Negative/Not performed |
| Parent(s) / Carer(s) tested for COVID |  Yes (if yes, free text) No |
| Parent(s) / Carer(s) COVID swab test | Positive/Negative/Not performed/ comment free text |
| Any history of operation postponment for medical reasons, excluding COVID |  Yes (if yes, free text) No |
| Any history of operation postponment because patient or family had COVID |  Yes (if yes, free text) No |
| Preoperative isolation | Yes (if yes, duration of isolation - 1 week, 2 weeks other) No |
| If yes, who was isolated | only patient, patient + one parent, patient + two parents |
| Family members in home, in addition to patient + 2 parents | family member ........... Isolated yes, no, free text |
|   | family member ........... Isolated yes, no, free text |
|   | family member ........... Isolated yes, no, free text |
|   | family member ........... Isolated yes, no, free text |
|   | family member ........... Isolated yes, no, free text |
| PPE worn by surgeon (select one or more) | Surgical Mask |
| FFP2 |
| FFP3 |
| Goggles |
| visor |
| powered respirator / hood |
| other |
| Surgical equipment (select one or more) | operating loupes |
| headlight |
| Microscope |
| none of the above |
| other |
| Comments on PPE + operating (select one or more) include free text with all options | No problems |
| Had to make modifications to allow use of loupes/headlight/microscope |
| uncomfortable |
| headache |
| fogging |
| impact on operative time |
| communication difficulties |
| Other |
| Operation date | DD/MM/YYYY |
| Time patient sent for | 00:00 |
| Anaesthetic start time | 00:00 |
| Anaesthetic end time | 00:00 |
| Operation start time | 00:00 |
| Operation end time | 00:00 |
| ET tube/LMA | Cuffed Rae |
| Uncuffed Rae |
| Cuffed re-inforced flexible tube |
| Cuffed other |
| LMA |
| Uncuffed other |
| Choice of ET tube/LMA Comments | Free text comments on choice of airway |
| Throat pack |  Yes (if yes, free text comment) No |
| Antibiotics |  Yes (if yes, choose one or more on induction, + ….doses) No |
| Grade of operating surgeon | SpR Fellow Consultant |
| Grade of assisting surgeon | SpR Fellow Consultant Other…...... |
| Post Op nursing | Ward (standard nurse to patient ratio)  |
| Ward "specialled" (1:1 or 1:2 ratio) |
| HDU |
| ITU |
| Any modification of anaesthetic: induction / intubation  |  Yes (if yes, free text comment) No |
| Any modification of anaesthetic: extubation  |  Yes (if yes, free text comment) No |
| Any modification of usual record collecting procedure (eg dental models/photos) |  Yes (if yes, free text comment) No |
| Any modification of surgical procedure  |  Yes (if yes, free text comment) No |
| Any modification of pre-surgical orthodontics  |  Yes (if yes, free text comment) No N/A |
| Post op NPA expected |  Yes (if yes, free text comment) No |
| Post op NPA used |  Yes (if yes, free text comment) No |
| Complications (select one or more. For each - Yes/No (if yes, free text comment)) | airway compromise |
| low O2 sats |
| haemorrhage |
| Wound infection |
| URTI |
| pneumonia/chest infection |
| dehiscence |
| fistula |
| secondary haemorrhage |
| other …........... |
| Date of discharge | dd/MM/YYYY |
| COVID diagnosis | Yes (swab positive) |
| Yes (suspected) |
| No |
| Post Op review (select one or more) | Phone date |
| Telemedicine date |
| Home visit date |
| Clinic visit date |

*Insert additional appendix and details or delete.*